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LARYNGEAL GRANULOMA, WITH SPECIAL REFERENCE TO CASES IN AUSTRALIA.[1]

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LARYNGEAL GRANULOMATA arise on or adjacent to the vocal cords and almost always result from trauma with abrasion of the glottic epithelium. It is convenient to divide the condition into two groups: the trauma may be endogenous in origin, being self-inflicted by such things as vocal abuse, or it may be the result of exogenous causes, the commonest being endotracheal anæsthesia.

The most vulnerable part of the cord is at the vocal process of the arytenoid cartilage, where the mucous membrane is thinnest and where the forcible approximation of these cartilaginous processes is compared by *Jackson and Jackson (1935) to a hammer and anvil. It is* at the vocal process, too, that abrasion of the mucous membrane by exogenous causes usually occurs. Whatever the cause of the abrasion, secondary infection follows. Perichondritis of the vocal process of the arytenoid often occurs. *Granulation tissue forms, and may enlarge to* produce a sessile protuberance, i.e., a sessile granuloma. By proliferation of the central tissue of the granuloma, and by healing at the periphery, the sessile mass may change into a pedunculated structure (Barton, 1953).

When the abrasion is of endogenous origin, it is usually bilateral, and the subsequent pathological changes take place very slowly, *sometimes over a period of years;* pedunculation rarely occurs, the usual picture being a sessile granuloma on one side and a shallow ulcer on the other.

When a granuloma originates from the more severe trauma of endolaryngeal manipulations, it may be unilateral or bilateral, and the changes occur more rapidly. *Spontaneous cure of granulomata sometimes occurs.*

Before preparing this paper, I sent out a circular letter to 125 Australian laryngologists, inquiring about their experience with this condition. This paper incorporates the information so obtained.

B. B. Blomfield, of Sydney, reports a case of a small granuloma, possibly post-operative in origin, on the tip *of the right vocal process, which subsided spontaneously,* leaving a congested area which finally healed completely. He also observed a small granuloma and contact ulcer in a priest, which healed with vocal rest.

Two instances of spontaneous cure of a pedunculated *granuloma have been reported (Clausen, 1932; El-Samma,*

[1] Presidential address delivered to the Section of Oto-Rhino-Laryngology, Australian Medical Congress (B.M.A.), Tenth Session, Hobart, March 1. to 7, 1958.

1950), the tumour having been coughed up when finally the thin pedicle had given way.

Microscopically, the granuloma is, at first, richly supplied with blood vessels and covered by an inflammatory exudate. The perichondritis of the vocal process may go on to necrosis. Later, fibrosis of the granuloma occurs, and it becomes more or less completely epithelialized.

Respiratory Tract Infection.

It is thought that respiratory tract infection predisposes to the formation of laryngeal granuloma.

T. G. Millar, of Melbourne, emphasizes the frequent existence of pharyngeal infection in cases of laryngeal granuloma arising from vocal abuse. He also quotes a case in which granulomata recurred twice after operative removal. The patient had chronically infected tonsils, from which *Staphylococcus aureus* was repeatedly cultured. The third removal of the granulomata was combined with tonsillectomy, after which the cords remained clear.

Patricia Davey, of Sydney, reports a case of granuloma at the anterior commissure, resulting from acute laryngitis with perichondritis of the thyroid cartilage.

Simson Hall (1946) considers that mild laryngitis or a slight cold may play a part in granuloma following endotracheal anæsthesia.

In this paper, I wish mainly to consider the post-operative cases, in which the lesion is the direct result of treatment for some other condition. The commonest cause of this group, as I have mentioned, is endotracheal anæsthesia, and the condition has been called "intubation granuloma". This term, however, does not cover all the reported cases.

Myerson (1956) has described two cases in which a granuloma developed after direct laryngoscopy without intubation. One patient had undergone two laryngoscopies, the first under local anæsthesia, and the second under general anæsthesia. The other patient had had three laryngoscopies, two under local anæsthesia, and one under general anæsthesia.

Incidence of Intubation Granuloma.

In the replies to my circular letter, 24 cases of post-intubation granuloma were reported. These, with the four cases reported by me in this paper, bring the Australian total to 28.

R. P. Rundle, of Townsville, North Queensland, reports two cases of laryngeal granuloma following bronchoscopy for bronchoscopic lavage in the treatment of bronchiectasis. The only available bronchoscope was old, with rough areas on its surface. These are the only two instances, so far as I know, of laryngeal granulomata resulting from bronchoscopy in Australia, although R. M. Glynn, of Adelaide, reports a case of ulceration over the right vocal process, which he saw two weeks after bronchoscopy had been performed.

However, endotracheal anæsthesia is the usual causative factor. Well over 100 such cases have been reported in various parts of the world. New and Devine (1949) consider the condition not as rare as it was believed to be on the basis of the published cases, and this belief is supported by investigation into cases in Australia. None had previously been reported here, but in addition to the 28 cases which form the basis of this paper, an indeterminate number of other cases have been referred to in replies to the circular, such as "a few cases following the use of Magill's tube", "granulomas seen occasionally after Magill's tube", "one or two cases which could be linked up with intubation of the larynx", "a fair number of cases caused by endotracheal anæsthesia", etc. A Sydney anæsthetist informs me that he has seen about 10 cases which he intends to report. I think that one can safely assume that over 50 cases of post-operative intubation granuloma have occurred in Australia.

Ætiology of Intubation Granuloma.

I wish now to consider in some detail various ætiological factors in intubation granuloma.

Sex.

Stephen Baker, of Tamworth, New South Wales, estimates that 80% to 90% of these patients are women. All my four patients were women. This is attributable to two factors: the smaller size and the thinner epithelium of the female larynx. The thickness of the epithelium of the vocal fold of a woman, which averages 59μ, is not much more than half the thickness of the vocal fold epithelium of a man, which averages 97μ.

Position of Head during Operation

The majority of cases occur after head and neck surgery, in which the head is usually in the extended or hyper-extended position. This places the larynx at a higher level than the head, which increases the static pressure of the curved Magill tube on the posterior part of the larynx. The posterior commissure thus becomes a fulcrum for the curved Magill tube.

H. Earnshaw, of Brisbane, points out that twisting of the head may lead to unilateral pressure by the tube on one cord. Ischæmia or abrasion may result.

Factors Concerning the Tube.

1. Size of the tube. It is generally agreed that large tubes are more likely to damage the glottic epithelium than small tubes. Hollinger, of Chicago, emphasizes the importance of avoiding the use of too large a tube. Flagg (1951) utilizes metallic tubes of seven sizes, ranging from 4 mm. outside diameter for very young children, to a maximum of 10 mm. outside diameter.

B. Hiller, of Hobart, uses a cuffed tube, maximum size 10 for men, and 8 for women. For children he uses a tube of a size equal to half the child's age.

Dwyer *et alii* (1949) examined a number of cases shortly after endotracheal anæsthesia, and found that the posterior third of each vocal cord often showed an area of congestion, which was more severe when a tube of large diameter had been used.

2. Shape of the tube. Many references are made to the curve of the Magill tube exerting maximum pressure on the posterior part of the larynx. This could, perhaps, be lessened or avoided by insertion of the hypopharyngeal pack in such a way that the tube is lifted forward, rather than pressed backwards.

A. S. de B. Cocks, of Adelaide, recommends the use of a double curved endotracheal tube, which lies further forwards in the larynx. Baker also raises the question of a double curved tube. In addition, Cocks points out that trauma to the cord may be caused by the small air tube for inflating a cuffed tube, if the small tube is on the outer surface. Nowadays, cuffed tubes are made with the small tube situated internally instead of externally.

3. Hardness of the tube. Thick-walled, hard, Magill tubes are more damaging to the epithelium than softer tubes. In one of my cases a straight gum elastic tube was used, showing that the Magill tube is not always culpable. Hardness of the tube, however, cannot be a very important factor, as Flagg's tubes are metallic.

In reply to a letter of mine, P. J. Flagg (New York) writes that to the best of his knowledge there has been no granuloma following the use of his endotracheal tubes for anæsthesia or for resuscitation in the new-born, in spite of his frequent requests that such cases should be reported to him.

4. Roughness of the tube. Tubes become roughened by wear, boiling, antiseptics, etc.

R. P. Rundle, of Townsville, Queensland, remarks that "if an old tube is examined through a magnifying glass one is horrified at its appearance". He states that old tubes of rubber or gum elastic develop transverse cracks, "which act like a rasp".

Jackson (1953) emphasizes the importance of care of the tube. He recommends checking for roughness of the tube

by inspection and careful palpation prior to use. Any suspicious spot is examined with a magnifying glass, and the tube, if necessary, is discarded.

Other possible irritative factors in connexion with the tube are its chemical composition, antiseptics used in sterilizing it and lack of proper lubrication. With regard to lubrication, it is important to use non-irritative lubricants.

5. Trauma during intubation. Hollinger emphasizes that trauma by introduction of the tube must be minimized in every possible way.

All authorities condemn "blind" intubation. Many emphasize the importance of complete relaxation of the glottis. Some recommend a preliminary spraying of the vocal cords with a local anæsthetic.

John H. Shaw, of Melbourne, reports a case of left-sided granuloma following thyroidectomy. The larynx and trachea were pushed to the right by the enlarged thyroid gland. Shaw postulates damage to the displaced left vocal process during intubation and pressure by the tube on it during the four-hour operation.

Introduction of the tube should, of course, be performed with careful attention to asepsis.

6. Movement of the tube. Both Mure Robertson, of Lismore, New South Wales, and Cocks refer to the cuff of the endotracheal tube being sometimes situated in the glottis opening, instead of below it. Cocks has seen this on several occasions. He states: "Apart from the changes in the patients' position, the drag of the heavy tubes connecting the Magill tube to the anæsthetic apparatus, may be a contributing factor in altering the position of the endotracheal tube. These tubes are frequently supported by being fixed to the pillow, to flimsy night clothes, or to the operating table drapes. I am confident that some better means of support could be devised . . ."

Laryngeal Movements.

1. Movements of the cords in the transverse plane. These occur in threatened laryngeal spasm and, more violently, in laryngeal spasm, coughing, vomiting and straining. They are prone to occur shortly after intubation in the "change-over" period from intravenous to inhalation anæsthesia, and also after the operation has concluded. If these movements occur when the tube is in the glottis, they imperil the glottic mucous membrane. Ideally, at the end of the operation, extubation should be carried out immediately before the return of the cough reflex.

2. Movements of the larynx in the long axis of the tube. These are associated with respiration and, to a lesser extent, with swallowing movements. The respiratory "tug" is most noticeable in deep anæsthesia with diaphragmatic breathing. If the tube is stationary, it will rub on the moving glottic epithelium. If the tube is not perfectly smooth, it will literally act, as Rundle says, like a "rasp".

On this subject Cocks states: "I am always pleased to see that portion of the endotracheal tube which projects from the mouth moving in concert with these vertical excursions of the larynx. If the tube is too rigidly fixed by strapping or other means, rubbing movements between the walls of the tube and the respiratory tract must occur."

3. Length of time that the tube remains in the larynx. The duration of the operation does not appear to be an important causative factor. However, two instances have occurred of the endotracheal tube, through oversight, being left *in situ* after the operation. In one case the tube was left in for 36 hours (personal communication), and in the other case for a week (Wilson, 1946). The first patient developed bilateral granulomata situated on the vocal processes. The second patient developed a unilateral granuloma.

Symptoms.

After endotracheal intubation, abrasion of the glottic mucous membrane may be suspected if the patient is hoarse. He may also complain of pain in the region of the larynx. Sometimes, hoarseness is not noticed for days, or even many weeks, after the operation.

The hoarseness is persistent. Sometimes there is an irritable cough. Occasionally, with bilateral granulomata there is dyspnœa. Extremely rarely, marked dyspnœa has necessitated urgent operative removal of the tumours (Kearney, 1946).

All my patients showed some degree of mental distress about their condition, and a good deal of tact was required in discussing it with them.

Diagnosis.

The appearance and site of the tumour are fairly characteristic. It is usually smooth, rounded, shiny and somewhat pink in colour. It varies in size up to a diameter of about 1 cm. However, a biopsy may be necessary to distinguish it from other inflammatory conditions, from benign and malignant neoplasms, and from laryngeal polypi.

Before discussing treatment I wish to report four cases which I have seen in my own practice.

CASE I.—Mrs. A., aged 64 years, was referred on November 10, 1952, by the late Dr. A. Holmes à Court, of Sydney. There was a history of tonsillectomy about four months previously, under endotracheal anæsthesia. A Magill tube, size 5 or 6 was used. Reactionary hæmorrhage necessitated a second endotracheal anæsthetic after an interval of about two hours, a similar Magill tube being used.

The patient complained of pain in the region of the larynx for two weeks after operation, and hoarseness ever since the operation. There had been some dyspnœa lately.

On examination, there were bilateral reddish-pink swellings on the vocal processes, sessile on the right and pedunculated on the left. The tumours were removed with cupped forceps under general anæsthesia on November 20.

The report of the pathologist (Dr. V. J. McGovern) stated that there was granulation tissue, partly covered by squamous epithelium. The diagnosis of granuloma was made.

Six weeks later, early recurrence (bilateral) was apparent. Four months after removal, the appearance of the larynx was exactly the same as before removal. The granulomata were again removed with cupped forceps, and the base of each was coagulated by a light application of diathermy. X-ray therapy was then carried out by Dr. E. W. Frecker, a dose of 1200*r* being given to each of the right and left laryngeal fields. No further recurrence followed, healing being complete.

CASE II.—Mrs. B., aged 40 years, was referred on April 10, 1956, by Dr. L. O. Rutherford, of Muswellbrook, N.S.W. There was a history of tonsillectomy 10 weeks previously, under endotracheal anæsthesia. The tube used was a gum-elastic catheter, size 20 (French). The duration of operation was 30 minutes. Two weeks after operation, she gave a sudden cough and felt "terrific" pain in the throat. From then on she had been hoarse. She occasionally noticed a clicking noise in the throat, with subsequent increase in hoarseness, which diminished again. Lately, she was dyspnœic on exertion.

On examination, there was a reddish-pink rounded swelling on each vocal process, the left being pedunculated and the right sessile. The granulomata were removed with cupped forceps on April 17, and the bases touched with a light application of diathermy.

The report of the pathologist (Dr. V. J. McGovern) stated that each lesion was a pyogenic granuloma. X-ray therapy was then carried out by Dr. Harold Ham. A dose of 2600*r* was given to the anterior aspect of the larynx, and a dose of 1200*r* given to the left lateral field. Healing was complete eight weeks later. There was no recurrence.

CASE III.—Mrs. C., aged 70 years, was referred on January 17, 1957, by Dr. F. Leventhal, of Sydney. There was a history of dental extractions under endotracheal anæsthesia three months earlier. A size 7 Magill tube, which was "old and soft", was used. The patient coughed twice before extubation. She complained of soreness in the region of the larynx after operation, and had had hoarseness for the last two months.

On examination, there was a reddish-pink sessile tumour over the vocal process of the right arytenoid, with an appearance strongly suggestive of granuloma. Biopsy was not performed. X-ray therapy was advised and carried out by Dr. P. M. C. Corlette, a dose of 1500*r* being given to each of the right and left lateral fields.

Subsequently, the tumour gradually decreased in size, healing being complete by July 3. Restricted use of the voice was permitted during the healing process.

Case IV.—Mrs. D., aged 45 years, was referred on June 28, 1957, by Dr. A. C. Herrington, of Bowral, N.S.W. She had a history of hoarseness for six weeks, and a feeling of pressure over the larynx for several months. Cholecystectomy had been performed on January 8 under endotracheal anæsthesia. The tube used was a Portex Magill tube, size 6 or 7. The duration of anæsthesia was one and a half hours.

On examination, there was a glistening, reddish-pink, pedunculated pea-shaped nodule, growing from the vocal process of the left arytenoid. The tumour was removed by cupped forceps under general anæsthesia on July 2.

The report of the pathologist (Dr. E. A. Shipton) stated: "Vascular granulation tissue, infiltrated by inflammatory cells. It is partly covered by squamous epithelium, but most of the surface is eroded. Granuloma pyogenicum."

After removal, silence was maintained for five weeks, at the end of which period smooth healing had taken place. There was no recurrence.

Prophylaxis.

Prophylaxis entails due regard for the many possible ætiological factors. Because of the relative rarity of the lesion, these ætiological factors are sometimes overlooked.

Can we foretell the likelihood of post-anæsthetic granuloma?

Hoarseness and pain in the region of the larynx within a day or two of operation are danger signals. Complete rest of the voice is then indicated. In addition, the patient should be warned against forcibly "clearing the throat", and coughing should, as far as possible, be controlled. Indirect laryngoscopy should be carried out. With laryngeal rest, the abrasion on the cord may heal. Healing may be assisted by the administration of a wide-spectrum antibiotic.

Treatment of Granuloma.

One hesitates to express very definite views on the treatment of granuloma with such a limited experience, but my present opinion on the subject is as follows.

Sessile Granuloma.

If the patient is first examined by the laryngologist when a sessile granuloma is present, complete vocal rest, etc., is indicated. Millar's experiences demonstrate that treatment of any concomitant respiratory tract infection may be necessary in some cases. If these measures are ineffective, radiotherapy then appears to offer the best chance of a cure. Operative removal, may, I think, be contraindicated at this stage because of the likelihood of recurrence. However, if the diagnosis is in doubt and a biopsy is advisable, the sessile granuloma can be carefully removed by cupped forceps flush with the line of the vocal cord. I suggest that this should be followed by a short course of radiotherapy.

Pedunculated Granuloma.

When pedunculation has occurred, the granuloma can be removed by cupped forceps, with the use of either direct or indirect laryngoscopy, and of either general or local anæsthesia. When the base of the granuloma is on the vocal process, instrumental removal probably should not be followed by application of the diathermy current, or by the electro-cautery or chemical caustics. All these would tend to cause or increase perichondritis or necrosis of the vocal process, and thus hinder healing.

I applied diathermy in two of my cases, but I consider that healing (aided by subsequent radiotherapy) occurred in spite of, and not because of, the diathermy.

After removal, complete laryngeal rest is necessary until healing is complete. The larynx should be examined regularly. The tendency to recurrence of these lesions is emphasized by many authorities, some patients having remained uncured after five operative removals. If a recurrence appears to be developing, the lesion should be given a short course of radiotherapy.

Conclusions.

What conclusions arise out of this investigation? Perhaps they can be summarized as follows:

1. The desirability of reporting these cases.
2. The importance of prophylaxis and of early recognition.
3. The usefulness of radiotherapy when the granuloma is sessile and also when a recurrence is threatening after operative removal.
4. The desirability of looking for, and if necessary, treating any concomitant respiratory tract infection.

Acknowledgements.

I wish to thank my many colleagues for their responses to the circular letter, and Dr. V. J. McGovern, Histopathologist to the Royal Prince Alfred Hospital, Sydney, for his help with pathological problems.

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OBSERVATIONS ON THE VENOM OF THE STONE FISH (SYNANCEJA TRACHYNIS).

By S. Wiener, Ph.D., M.B., B.S.,[1]

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Only three experimental investigations have been published on the properties and toxicity of the venom of the stone fish.

The first studies were published by Bottard in 1889. From a live stone fish, he aspirated the contents of one venom gland, and injected three drops subcutaneously into a dog weighing 14 kg. The animal showed signs of pain, incontinence of urine, tremors, ruffling of hair, anorexia and thirst. The skin at the site of injection became necrotic. Sixteen days later the dog had fully recovered. The injection of venom into four frogs produced motor and sensory paralysis and death within a period of three hours. Bottard also injected a drop of venom into his leg, and suffered severe pain and parasthesia at the site of injection, which became avascular and necrotic. Ten years later a scar was still present at the site of injection.

In 1928, Duhig and Jones reported the effects of the subcutaneous injection of stone-fish venom into three

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guinea-pigs. The animals showed evidence of pain, tremors, motor paralysis and dyspnœa. Two of the animals recovered completely. The third animal was anæsthetized when respiratory movements had become almost imperceptible. In this animal, electrical stimulation of the sciatic nerve and leg muscles produced contraction of the muscles. These authors also found that stone-fish venom was hæmolytic to red blood cells of various species of animals.

More recently, Gail and Rageau (1956) have reported their observations on the effects of stone-fish venom in animals. A frog injected with the contents of one venom gland died four hours later with extensor paralysis of the hind limbs. The heart continued to beat for one hour afterwards. A rat injected subcutaneously with the contents of two glands showed signs of severe pain, dyspnœa, muscular spasms, weakness and intense thirst. A hæmatoma developed at the site of inoculation, and the animal died 16 hours after the injection. Serous fluid was present in the pelvic regions. A dog weighing 9 kg. was injected subcutaneously with the contents of five venom glands. Almost immediately afterwards the animal had spasmodic convulsions and dyspnœa, and lost consciousness. Death, which occurred suddenly one minute after the injection, was attributed by the authors to respiratory arrest and paralysis of the heart.

Through the cooperation of Mr. G. Coates, of Townsville, we were able to obtain a sufficient number of stone fish for further studies to be carried out on the toxicity and other properties of stone-fish venom. The studies, which are reported in the present paper, were necessary before an antivenene against stone-fish venom could be produced. Included amongst these are observations which have a bearing on the non-specific treatment of stone-fish stings in man. The method of producing stone-fish antivenene will be presented in a subsequent paper.

Source of Material and Venom Yield.

Live stone fish were transported by air from Queensland in closed containers without water. Provided a fish was in good condition when despatched from Queensland, it generally survived its ten-hours' journey without apparent ill-effects. On arrival in the laboratory it was transferred into a large glass vessel containing artificial sea water, through which oxygen was bubbled continuously.

The next morning the live fish was immobilized on a wooden board, and the two venom glands on each of the 13 dorsal spines (Figure I) were dissected free from the surrounding tissue. Care had to be exercised to avoid pressure on the glands which caused the ejection of venom. Each spine with the venom glands attached was cut off near its base and inverted over a watch glass. Pressure on the venom glands with a pair of forceps resulted in venom spurting out and dripping from the tip of the spine into the watch glass. Alternatively, venom could be aspirated and collected from the glands with a needle and syringe. A full venom gland may contain 0·03 ml. of fluid.

The collected venom from all the spines of one fish was pooled and freeze-dried. Table I sets out the venom yield obtained in this way from seven stone-fish. The average yield of venom per spine ranged from 5·1 mg. to 8·8 mg. However, as not all the venom glands on the spines of a fish were equally full, the amount of venom in individual spines must have shown a greater range than that. On one occasion the contents of the two venom glands of the third spine, which appeared exceptionally large and full of venom, were dried separately, and 9·8 mg. of venom were obtained. Nearly every fish had one or more spines which carried a thin strand of what appeared to be connective tissue in place of a filled venom gland (Table I).

Microscopically, a drop of fresh venom was found to be very cellular. The cells, which were in clusters, had a hyaline appearance, and nuclei were visible in only a few of them. When water was added, a granular precipitate was found in the fluid surrounding the cells. With iodine, two types of cells became differentiated: a few cells measuring 30 to 40 μ in diameter, filled with a coarse granular dark brown precipitate, and more numerous smaller cells measuring 10 to 12 μ in diameter, which stained a golden yellow colour with iodine. These cells also had darker staining areas. Phloxine, gentian violet, Giemsa and Wright stain were also taken up by the cytoplasm of the cells. On the other hand, methylene blue, gentian violet or Sudan III did not stain the cells.

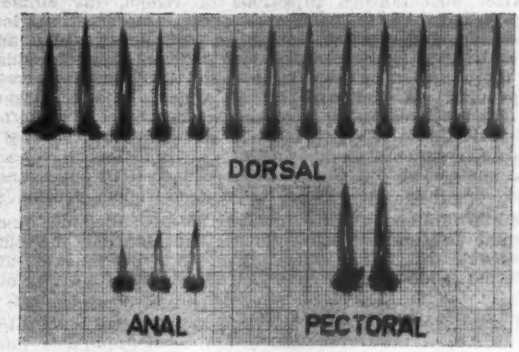

FIGURE I.
Venom spines of stone fish.

Toxicity in Laboratory Animals.

Solutions of venom were made up by dissolving dried venom in normal saline solution buffered at pH 7·4. When dried venom was dissolved in the diluent, not all of it dissolved, and before use it had to be centrifuged. Of the weight of venom originally added, 25% to 30% remained in the precipitate, which partly consisted of cellular material. The lethal doses of venom which are given below for the different animals were based on the amount of venom used to make up the solution. In terms of the actual amount of venom injected, they were 25% to 30% lower.

TABLE I.
Venom Yields from Stone Fish.

No.	Weight of Fish. (Grammes.)	Height of Fish. (Inches.)	Length of Fish. (Inches.)	Number of Spines with Venom Glands.	Total Weight of Venom. (Mg.)	Average Weight of Venom/ Spine. (Mg.)
1	800	3·5	11·0	12	62·0	5·1
2	750	3·5	10·0	10	65·0	6·5
3	580	3·5	9·5	10	46·8	4·7
4	570	3·5	9·5	8	49·0	6·1
5	735	3·5	10·5	10	88·4	8·8
6	830	3·5	10·5	11	64·9	5·2
7	768	3·0	10·0	10	60·0	6·0

Toxicity in the Mouse.

The signs produced when stone-fish venom was injected into mice depended on the dose and the route of injection. After an intravenous injection of lethal amounts of venom, the following signs were observed: incoordination, paralysis of hind limbs, irregular respiration, coma, convulsions, and cessation of respiration followed by cardiac arrest. Before death, frothy fluid, often blood stained, welled out profusely from the nose. At post-mortem examination, the ventricles were contracted, and the lungs were found to be hæmorrhagic, gelatinous in consistency and filled with frothy fluid. Blood collected after death clotted normally, and there was no hæmolysis. After an intravenous injection of four or more lethal doses of venom, the animal fell on its side, gave a few kicks and gasps, and died within a few seconds. With smaller amounts of venom, death occurred

in 60 to 100 minutes after the injection. When one lethal dose of venom was injected, death occurred within three to four hours and rarely overnight. Table II shows the results of one assay. With sublethal doses of venom, the animals were very quiet, were reluctant to move and had difficulty in keeping their heads up. With different batches of venom, the intravenous LD_{50} lay in the range of 0·005 mg. to 0·01 mg. per mouse weighing 15 grammes.

After subcutaneous injections of venom, the animals appeared to be in pain, developed incoordination, lost sensation and became comatose with bradycardia and slow and irregular respiration. Death was heralded by the cessation of respiration followed by cardiac arrest. Depending on the amount of venom injected, death occurred between one hour and twenty-four hours after the injection. At post-mortem examination, there was a hæmorrhagic area at the site of injection, the heart was contracted, but the lungs were normal in appearance. The LD_{50} dose was 0·04 to 0·06 mg. of venom per mouse.

Signs following an intraperitoneal injection were similar to those which followed subcutaneous injection. However, in mice which died, the peritoneum and internal abdominal organs were congested and hæmorrhagic. The LD_{50} dose was from 0·02 to 0·03 mg. of venom per mouse (Table II).

TABLE II.

Toxicity of Stone-Fish Venom (Batch 3) in Mice.

Amount of Venom. (Mg.)	Intravenous Injection.		Intraperitoneal Injection.	
	Number of Mice.	Number that Died.	Number of Mice.	Number that Died.
0·0025	5	0	—	—
0·005	5	1	—	—
0·0075	5	3	—	—
0·01	5	5	5	0
0·02	5	5	5	0
0·03	5	5	5	3
0·04	—	—	5	4
0·06	—	—	5	5
0·08	—	—	5	5
0·10	—	—	5	5

Mice showed no irritability when stone-fish venom was injected intracerebrally. With lethal doses of venom, the animals became weak and paralysed, and were immobile until death occurred. With a sublethal dose of venom, mice which appeared even severely affected completely recovered. The LD_{50} dose of venom by this route was 0·004 mg.

Guinea-Pig.

The effects of stone-fish venom in the guinea-pig depended on the amount of venom injected. Guinea-pigs weighing 250 grammes were used.

The injection of 4 mg. of venom into the subcutaneous tissues of the back produced weakness of the legs, slowing of movement, depressed respiration, coma and death in three hours. On post-mortem examination, there were petechial hæmorrhages of the skin at the site of injection, and there was blood-stained fluid in the thorax; the lungs were emphysematous, the abdominal organs were congested and the left adrenal gland was hæmorrhagic.

The subcutaneous injection of 2 mg. of venom produced weakness of the legs; the next day œdema and redness were present at the site of injection, with patchy necrosis of the skin and loss of hair. Death occurred on the third day. The skin at the site of injection was necrotic and adherent to the underlying tissues. The lungs were congested, hæmorrhagic and collapsed. The right side of the heart was dilated, and the mesenteric vessels were engorged with blood. There was also congestion of the left suprarenal gland. There was no hæmolysis of blood removed from the heart.

When 1 mg. of venom was injected subcutaneously, there was no weakness of the legs, but 24 hours afterwards the skin at the site of injection was red and swollen, showing through the hairs, which appeared to be in clumps. On the fifth day there was a well-developed area of necrosis, measuring two inches by one and a half inches, and surrounded by a narrow zone of erythema. On the sixth day the animal died. The reflected skin at the site of injection was adherent to the underlying muscles by a fibrinous exudate.

The subcutaneous injection of 0·6 mg. of venom into a guinea-pig produced necrosis of the skin at the site of the injection. By the seventh day there was a well-defined zone of demarcation around the necrotic area (Figure II); otherwise, apart from some loss of

FIGURE II.

Necrosis of skin of guinea-pig after a subcutaneous injection of stone-fish venom.

weight, the animal did not appear to be adversely affected. However, on the morning of the eleventh day, the animal was found to be in a coma, and death occurred in the afternoon of the same day. There was some fluid in the peritoneum, and there was fibrinous exudate on the spleen and kidneys. Both adrenals were congested. The lungs were of normal appearance, but the heart was dilated. The bladder was filled with cloudy urine, 2 ml. of which were aspirated with a syringe. The cloudiness cleared with acetic acid, and tests for albumin and reducing substances gave negative results.

The injection of 0·2 mg. of venom produced necrosis of the skin, but the animal did not die.

The hæmorrhagic effect on the suprarenal glands, which was observed in some of the animals which died, resembled that produced by diphtheria toxin. However, as this was at times unilateral and was always associated with hæmorrhages in the surrounding subcutaneous tissues where the injection was made, it appeared to be due to the direct effect of venom diffusing from the site of injection.

Rabbit.

Ten minutes after an intradermal injection of venom into a rabbit, the injected area developed a greenish-purple colour as seen in a bruise, and was surrounded by a rim of pale skin. A wheal remained at the site of injection, and 24 hours later it had become pale and avascular. It was surrounded by purpuric spots and a

zone of erythema. The diameter of the avascular area varied with the amount of venom injected (Figure III). There was no œdema. During the next few days, necrosis of the injected area occurred. The area of necrosis was smaller than the area of ischæmia present on the second day. With smaller amounts of venom, the avascular area gradually decreased without the development of necrosis. This ischæmic action of the venom could be used for assaying the toxicity of venom (Table III); 0·002 mg. of venom in a volume of 0·05 ml. constituted the minimum skin ischæmic dose for the rabbit.

Dog.

The effect of stone-fish venom on the blood pressure and respiration of the anæsthetized dog was recorded graphically (Figures IV, A, B, C).

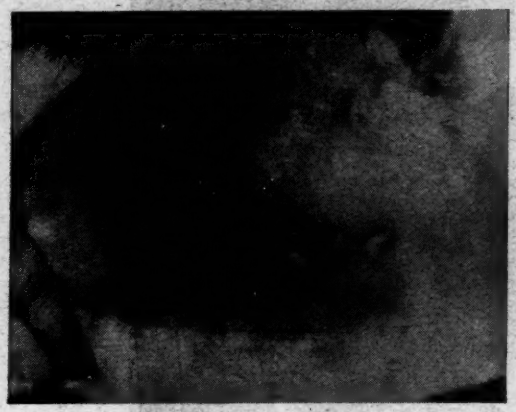

FIGURE III.
The ischæmic and necrotic effects of stone-fish venom after intradermal injection in a rabbit.

The intravenous injection of 3·5 mg. of venom into a dog weighing 8 kg. produced cardiac and respiratory arrest in less than two minutes (Figure IV A).

The injection of 1 mg. of stone-fish venom produced a rise in blood pressure followed by a fall. During this fall the pulse pressure was trebled. During the next 20 minutes, the blood pressure gradually increased, and when it was back to normal at the end of this period, the pulse pressure also suddenly returned to its original level. Whilst the blood pressure was reduced, respirations became deeper and somewhat irregular (Figure IV B).

The injection of 1·5 mg. of venom, which had been stored for several days at 4° C., produced a rise in blood pressure, which returned to normal at the end of five minutes. There was also a short period of apnœa (Figure IV C).

TABLE III.
The Intradermal Injection of Varying Amounts of Stone-Fish Venom in the Rabbit.

Amount of Venom (Mg.) in a Dose Volume of 0·05 Ml.	Diameter of Circle of Ischæmia 24 Hours Later. (Mm.)	Ten Days Later.
0·050	17	Necrosis.
0·025	15	Necrosis.
0·012	14	Necrosis.
0·006	11	Necrosis.
0·003	6	Healed.
0·0015	2	Healed.
0·0008	0	—
0·0004	0	—

Fowl.

The intravenous injection of 0·5 mg. of venom into an anæsthetized fowl weighing 2·5 kg. caused within two minutes a fall in blood pressure from 200 mm. of mercury to almost zero. The blood pressure rose back to normal during the next minute, but then fell again to 80 mm. of mercury. At this level it stayed for 10 minutes, when a further injection of 1 mg. of venom killed the bird in four minutes (Figure V A).

After an intravenous injection of 0·1 mg. of venom, the blood pressure fell to about 100 mm.; it gradually increased, and returned to normal half an hour after the the injection (Figure V B).

Properties of Venom.

Fresh stone-fish venom was opalescent and had a pH of about 6·0. The addition of water or saline solution produced a precipitate. When this was removed and the clear supernatant allowed to stand at room temperature or at 4° C., it became opalescent and a new precipitate formed. This repeated formation of a precipitate when solutions of stone-fish venom were stored was associated with a progressive loss of toxicity.

Freeze-dried venom, which had been stored in a desiccator over silica gel for three months, did not show any appreciable loss of toxicity.

Stone-fish venom gave all the reactions of a protein. It was precipitated by mineral acids, alcohol and picric acid. No reducing sugars were present after hydrolysis. A copious precipitate was produced on boiling.

The heating of venom at 50° C. for five minutes produced a fine precipitate with complete loss of toxicity. This enabled a mouse to tolerate 0·7 mg. by the intravenous route without ill effects. Venom heated to 50° C. had also lost its necrotic action on the skin of rabbits, and in the fowl no longer exerted a hypotensive effect, but instead caused a rise in blood pressure (Figure VI).

Below pH 4 the toxicity of the venom was completely destroyed almost instantly. About 50% of the toxicity was destroyed at pH 8·6 in three hours, whilst after 24 hours almost all the toxicity was destroyed. A solution of venom was most stable between pH 7·0 and pH 7·6, and could be stored at 4° C. for 24 hours with only slight reduction in toxicity. However, when stored for 48 hours, there was a reduction in toxicity by 50%, whilst four to five days' storage caused complete loss of toxicity.

Freezing and thawing increased the rate at which stone-fish venom lost its toxicity. Similarly, the adverse effect of changes of pH on the stability of venom was enhanced when the temperature was increased.

Stone-fish venom hæmolysed the red blood cells of the guinea-pig, but even with 1·8 mg. of venom the hæmolysis of 0·2 ml. of a 3% suspension of red cells was not complete.

On one occasion, non-pathogenic gram-positive diplococci were cultured from the contents of a venom gland.

Antigenicity.

Stone-fish venom was antigenic in the mouse, rabbit and horse. In the rabbit and horse, both precipitating and neutralizing antibodies were produced. The antivenene produced in the horse has been refined and concentrated, so that 1 ml. neutralizes 10 mg. of venom. This antivenene is now awaiting clinical trial. When antigen and antibody reacted in agar by diffusion, two well-defined lines were produced, suggesting that stone-fish venom contains at least two antigenic components.

Venom which had lost its toxicity either as a result of exposure to a low pH or by freezing and thawing was no longer antigenic.

Detoxification of Venom by Various Substances.

The toxicity of stone-fish venom was destroyed, not only by changes of pH and temperature, but also by the addition of a variety of substances.

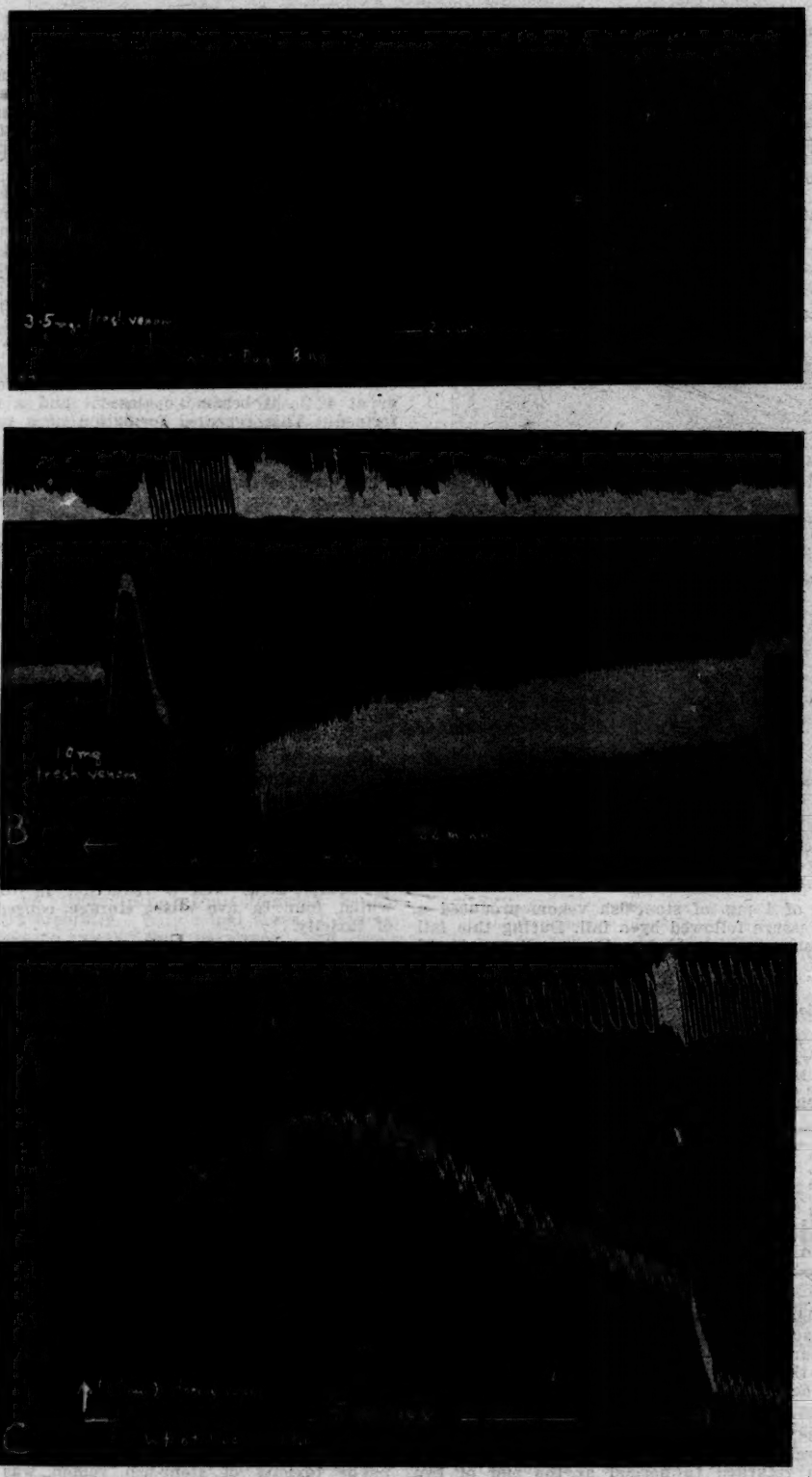

FIGURE IV.

The effects of stone-fish venom on the blood pressure and respiration of the dog (upper tracing, respiration; lower tracing, blood pressure).

It has been reported previously (Wiener, 1958) that emetine hydrochloride neutralized one lethal dose of venom. Further investigations revealed that this neutralizing effect was due to the low pH in which solutions of emetine are dispensed. The solution which we used had a pH of 4·2.

However, a number of dyes and other substances in solutions buffered at pH 7·4 destroyed the toxicity of stone-fish venom. The following substances exerted such an effect: methyl violet, phloxine, pontamine sky blue, hydrogen peroxide, iodine, potassium permanganate and sodium oleate. No loss of toxicity was observed when the following dyes were added to stone-fish venom: methylene blue, basic fuchsin, eosin, gentian violet, neutral red and alizarin. In these experiments, 0·05 ml. of an approximately 0·5% solution of the different substances was added to 14 lethal doses of venom and injected immediately afterwards into mice by the intravenous route. In the concentrations used, the various substances alone were not toxic to mice.

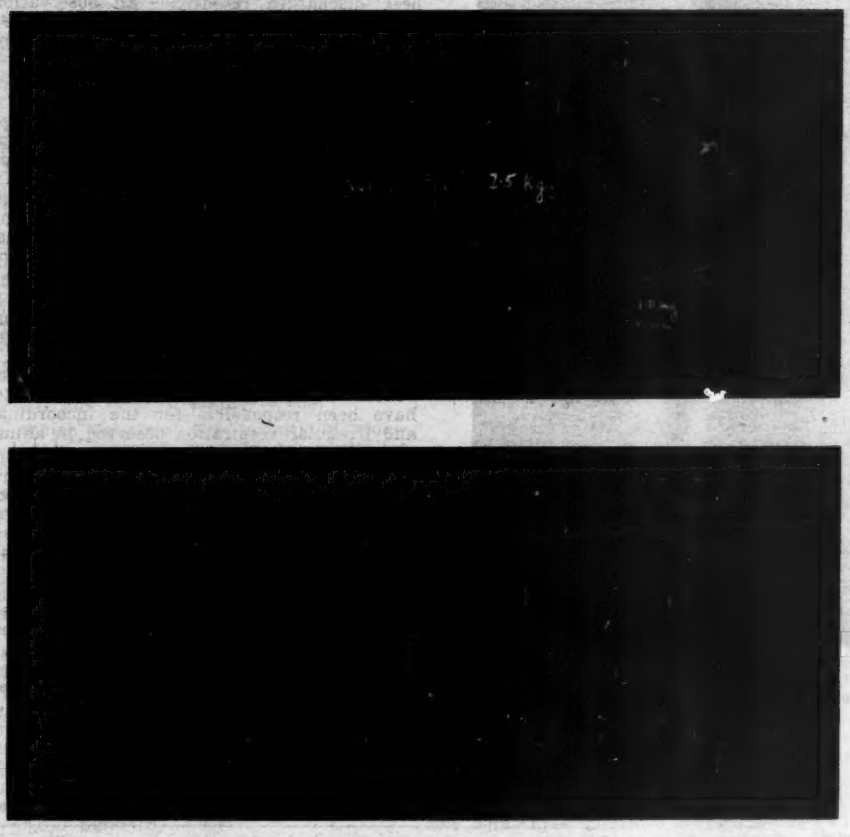

FIGURE V.
The effect of fresh stone-fish venom on the blood pressure of the fowl.

The neutralizing action of potassium permanganate and congo red on stone-fish venom was studied further. To 20 lethal doses of stone-fish venom, equal volumes of different dilutions of these two substances were added, and the mixtures were injected immediately into mice by the intravenous route. From Table IV it can be seen that 0·008 mg. of potassium permanganate neutralized 0·095 mg., or about 12 times its own weight of stone-fish venom; congo red neutralized about six times its own weight of venom. The detoxifying effect of congo red and potassium permanganate appeared to be immediate, since the same results as those given in Table IV were obtained in a parallel experiment when the mixtures were allowed to stand for 15 minutes at room temperature before being injected.

To test the possibile therapeutic application of this neutralizing effect of potassium permanganate and congo red, a number of mice were injected intraperitoneally with six lethal doses of stone-fish venom. At varying periods of time after the injection of venom, 0·5 ml. of a 1:1000 solution of potassium permanganate or congo red, buffered at pH 7·4, was also injected intraperitoneally. The mice were allowed to run around freely between injections. From Table V, which gives the results of one such experiment, it can be seen that when potassium permanganate was injected not later than three minutes after the injection of venom, the animals survived. Congo red protected when injected up to seven minutes after the injection of venom. These experiments, which have been repeated several times, showed that the protective effect of potassium permanganate ranged from three to six minutes, and for congo red from seven to 13 minutes after the injection of venom. The superior action of congo red over potassium permanganate might have been caused by the inactivation of potassium permanganate in the presence of tissue fluids, whilst the variations observed in the results of duplicated experiments were largely due to the inconstant rate at which venom was absorbed in individual mice after intraperitoneal injections.

The in-vivo protective effect of both potassium permanganate and congo red was the result of their direct action on venom in the peritoneal cavity of the mouse. After lethal amounts of venom had entered the circula-

tion, neither substance protected. Amounts of congo red injected intravenously and sufficient to make the skin of mice pink, did not protect against a subsequent intraperitoneal or intravenous injection of even one lethal dose of venom.

Discussion.

Under natural conditions, stone fish must be exposed occasionally to the atmosphere for varying periods of time when the waters amongst the reefs where they are found recede with the tide. The accessory respiratory mechanism which the stone fish have evolved (Bottard, 1889) enabled them to live without water for 10 hours whilst they were transported from Townsville to Melbourne.

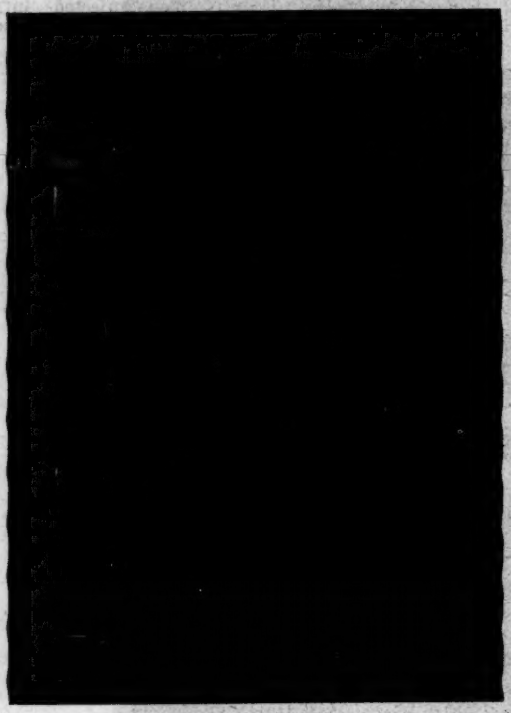

FIGURE VI.
The effect of heated stone-fish venom on the blood pressure of the fowl.

The presence of spines which appeared to have no venom glands provides an explanation for those cases of stone-fish sting in man which were not followed by any serious effects (Flecker, 1956). It is possible that in these spines, venom glands were congenitally absent, had ruptured and atrophied or their contents had been discharged recently. An observation reported by Bottard (1889) suggests that venom once discharged is not regenerated at all or only very slowly.

The function of the venom in the living animal remains unknown. Unless the otherwise inactive stone fish possesses an unsuspected ability of movement, it cannot use its venom for killing prey, since the injection of venom into another animal can take place only after the animal has been pierced by the spine and some pressure has been exerted on the venom glands. It is more likely that the stone-fish uses its venom for protection, although its formidable spines and its effective camouflage would seem sufficient protection. However, stingrays also carry venom in their caudal spine (Russell and Harreveld, 1956).

The varied manifestations, such as pain, necrosis, hypotension and increase in capillary permeability, which could be observed after the injection of stone-fish venom into animals, appeared to have been caused by a peripheral action of the venom. A central action of venom was less clearly defined, but it appeared to have been responsible for the incoordination, paralysis and irregular respiration observed in animals.

The hypotensive effect of stone-fish venom might have been due to a lowering of peripheral resistance as a result of dilatation of arterioles. The associated increase in pulse pressure, which was observed in the dog, is consistent with such a view. However, a direct toxic effect on cardiac muscle cannot be excluded. Such an effect has been observed with the venom of the stingray (Russell and Harreveld, 1956). In addition, the avascular appearance of the skin, which preceded necrosis when stone-fish venom was injected intradermally, indicates that vasoconstriction also occurred. The attacks of syncope which follow stone-fish stings in human cases may be the result of hypotension or due to the severe pain.

TABLE IV.

The Neutralization of Stone-Fish Venom by Different Concentrations of Potassium Permanganate and Congo Red.

Substance Tested.	Quantity of Potassium Permanganate (Mg.) or Congo Red Added to 0·1 Mg. of Venom.[1]								
	0·25	0·12	0·06	0·03	0·015	0·008	0·004	0·002	0·001
Potassium permanganate ..	s[2] s	s s	s s	s s	s s	s s	d[2] d	d d	d d
Congo red		s s	s s	s s	s s	d d	d d	d d	d

[1] Mixtures made up to constant volume and 0·6 ml. of each injected intravenously into two mice.
[2] s = survived.
[2] d = died.

TABLE V.

Protective Effect of Potassium Permanganate and Congo Red Injected Intraperitoneally into Mice at Varying Times after an Intraperitoneal Injection of Stone-Fish Venom.

Substance Injected (0·5 ml. of 1 : 1000).	Time (Minutes) after Injection of 0·2 mg of Venom.									
	1	2	3	5	7	9	12	14	16	18
Potassium permanganate	s s[1]	s s	s s	d[2] s	dd	dd	dd	dd	dd	dd
Congo red ..	s s	s s	s s	s s	sd	ss	dd	dd	dd	dd

[1] s = survived.
[2] d = died.

The acute pulmonary œdema observed in mice was due either to an increase in the permeability of capillaries, or to failure of the heart. Damage to capillaries was responsible for the hæmorrhagic effects of the venom and the presence of fluid in serous cavities.

Duhig and Jones (1928), using a suspension of stone-fish venom containing cellular elements, observed an apparently high hæmolytic activity against guinea-pig red blood cels. Our venom solution, which was free from cells, was only weakly hæmolytic. The absense of hæmolysis in the blood of animals which had died from the effects of stone-fish venom makes it unlikely that hæmolysis played a significant part in the manifestations of stone-fish venom intoxication.

The protein nature of stone-fish venom and its sensitivity to physical and chemical agents suggest that it has a relatively high molecular weight and accounts for its excellent antigenicity. Although solutions of dried venom were most stable between pH 7·0 and 7·6, fresh venom had a pH of about 6·0. It is possible that the cellular components of venom protect it against deterioration.

Potassium permanganate destroyed the toxicity of stone-fish venom by virtue of its oxidizing action. It has a similar effect on snake venom (Bannerman, 1914).

Congo red, which neutralized stone-fish venom, has also been found to antagonize the action of curare (Kensler, 1949). It precipitated the toxic fraction of the venom of the Sydney funnel-web spider (Wiener, 1957), but there was no loss in toxicity. The action of dyes on animal venoms are complex, and deserve further study.

Sodium oleate, which destroyed the toxicity of stone-fish venom, has been reported recently to neutralize staphylococcal toxin (North and Doery, 1958).

The neutralization of stone-fish venom by potassium permanganate and congo red offers some means whereby venom which has not been absorbed can be destroyed locally.

We have previously recommended the local injection of a solution of potassium permanganate for the treatment of stone-fish stings in man (Wiener, 1958). It is likely that in tissues, a solution of congo red injected into the site of the sting is even more effective than potassium permanganate in destroying venom that has not been absorbed. In addition, a number of other dyes and oxidizing agents and any solution of which the pH is below 4 and above 9 may act similarly, and thus provide a possible explanation for the alleged effectiveness of a great variety of plant extracts which natives have used for the treatment of stone-fish stings.

Summary.

A method is described for obtaining venom from the dorsal spines of the stone fish. The yield of dried venom per fish ranged from 49 mg. to 88 mg.

Stone-fish venom was toxic to mice, guinea-pigs, dogs and fowls. The dose of venom and its route of injection influenced the manifestations of intoxication, which are described in detail.

The injection of stone-fish venom into animals produced the following effects: pain, necrosis of the skin, irregular respiration, bradycardia, pulmonary œdema, incoordination, weakness, paralysis, hypotension and in increase in capillary permeability.

In mice, the LD_{50} dose of venom when injected intracerebrally, intravenously, intraperitoneally and subcutaneously was 0·004 mg., 0·007 mg., 0·03 mg. and 0·05 mg. respectively.

Stone-fish venom behaved as an unstable protein; its toxicity was destroyed by repeated freezing, by heating at 50° C., and by changes of pH. It was also antigenic.

Oxidizing agents and certain basic and acid dyes destroyed the toxicity of venom.

In mice, potassium permanganate and congo red neutralized the toxic action of stone-fish venom in vivo under certain conditions.

The significance of these findings in relation to stone-fish stings in man are discussed.

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BLOOD PRESSURES IN AUSTRALIAN ABORIGINES.[1]

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MANY observations have been made on different ethnic groups with regard to blood pressure, diet, environment and heredity. Kean and Hammill (1949) review some of them in discussing the anthropology of arterial tension. They point out the need for a more extensive and accurate gathering of such data. Discussing the Australian aboriginal, they state that studies on him are "thoroughly inadequate and we can draw no conclusions from them". The present study was undertaken in an attempt to correct this state of affairs.

The observations come from a number of sources. There are only three published series: Hicks and Matters, 1933, Hicks *et alii*, 1934, and Nye, 1937. Dr. G. Croll very generously let me use some 1500 readings that he, with some help from Mr. W. Hartley, took while on a leprosy survey for the Queensland Department of Public Health in 1938. Dr. D. I. B. Kerr allowed me to quote some figures taken at Yuendumu in 1951, and Dr. L. O. S. Poldevin gave me some he took there in 1956. Finally, I observed values at Haast's Bluff Mission in 1956 and 1957, and at "The Bungalow" settlement and Alice Springs Hospital in 1957.

Material and Methods.

The pressures were taken by mercury or checked aneroid manometers. They were usually taken with the subject in the sitting position, but some observers used the lying position (Hicks and Matters, 1933; Hicks *et alii*, 1934; Crosby and Kerr, 1951, personal communication). Their figures are included with the rest, since Brigden *et alii* (1950) showed that postural changes produce only minor alterations in pressures. The conditions under which the pressures were recorded may have caused some apprehension in the aborigines. In most

[1] Some of the data upon which this paper is based were collected on University of Adelaide Anthropological Expeditions financed mainly by the Wenner-Gren Foundation for Anthropological Research, New York, and the Adelaide University Medical Research Fund.

TABLE I.
Individual Statistics.

Place.	Sex.	Systolic Pressure.									Diastolic Pressure.									Observer.
		No.	Mean a Pressure	Mean Age. (Yrs.)	Σxy[1]	Σy^2[2]	Σx^2[3]	a[4]	b[5]	P[6]	No.	Mean a Pressure.	Mean Age. (Yrs.)	Σxy	Σy^2	Σx^2	a	b	P	
Haast's Bluff ..	M.	44	116·77	39·045	−754·55	5697·7	13291·0	116·73	−0·05677	NS[7]	49	75·878	34·745	−1266·5	6617·3	17703·0	75·503	−0·07154	NS	Casley-Smith (1956).
	F.	67	115·55	25·591	1547·4	7849·6	15057·0	113·08	0·1028	NS	62	77·581	26·113	2541·9	5537·1	12039·0	79·713	0·2112	x[8]	
Haast's Bluff ..	M.	28	117·32	27·000	737·50	5549·1	2925·0	120·59	0·2521	NS	29	77·931	26·224	1003·5	3075·9	2437·9	83·601	0·4116	x	Casley-Smith (1957).
Bungalow	M.	20	132·00	41·500	1520·0	3320·0	3820·0	131·40	0·3979	NS	18	90·026	44·500	1100·0	2648·7	3800·0	88·725	0·2895	NS	Casley-Smith (1952).
	F.	19	115·79	39·763	1371·1	2263·2	4673·7	115·86	0·2934	NS	20	75·250	38·500	180·00	1908·8	4480·0	75·310	0·04018	NS	
Cockatoo Creek ..	M.	36	108·61	37·278	5038·9	4830·6	10922·0	108·74	0·4613	xx[9]	36	74·028	36·444	3768·1	3166·0	11364·0	75·548	0·3316	xxx[10]	Hicks and Matters (1933).
	F.	11	102·27	30·864	1090·9	1393·2	2654·5	106·03	0·4110	NS	11	68·636	29·955	−268·18	929·55	247·7	67·503	−0·1085	NS	
Mt. Leibig	M.	20	109·75	37·000	−137·50	948·75	4575·0	109·84	−0·03006	NS	20	73·250	37·000	987·50	1338·7	4575·0	73·807	0·2159	NS	Hicks *et alii* (1934).
Yuendumu ..	M.	26	120·89	41·038	851·9	4441·4	8388·5	120·78	0·1016	NS	24	85·213	42·417	541·67	1781·3	7595·8	83·174	0·07131	NS	Crosby and Kerr (1951).
	F.	9	126·00	37·833	−216·67	538·89	3200·0	125·85	−0·06776	NS	9	85·444	32·278	−3·444	655·56	8155·6	84·601	−0·1092	NS	
Yuendumu ..	F.	56	102·77	29·680	−802·68	10221·0	3798·2	100·58	−0·2113	NS	55	71·727	29·591	−1333·6	3585·9	3974·6	68·234	−0·3356	x	Poldevin (1956).
Lockhart Creek ..	M.	63	135·22	58·152	708·84	—	5260·3	132·79	0·1348	NS	63	76·825	58·151	−1060·9	—	5260·3	80·585	−0·2072	NS	Nye (1937).
	F.	40	129·85	58·000	881·00	—	3910·0	125·90	0·2253	NS	40	77·525	58·000	−233·50	—	3910·0	78·603	0·1927	NS	
Mona Mona ..	M.	54	143·80	35·537	7552·4	19272·0	10608·0	146·98	0·7120	xxx	54	82·500	35·537	3100·0	7912·5	10608·0	83·807	0·2922	xx	Croll (1933).
	F.	76	148·22	31·855	11903·0	29660·0	21837·0	147·67	0·5451	xxx	76	82·303	31·855	4292·8	7547·0	21837·0	83·904	0·1966	xxx	
Yarrabah	M.	155	136·42	32·403	12781·0	42263·0	31754·0	139·48	0·4025	xxx	157	79·236	32·303	11031·0	16208·0	31877·0	81·901	0·3461	xxx	Croll (1933).
	F.	173	135·20	29·772	17790·0	64918·0	38314·0	139·95	0·4643	xxx	175	79·857	29·711	8250·3	23046·0	40369·0	81·960	0·2044	xxx	
Cowel Creek ..	M.	51	131·08	37·598	−2150·4	10891·0	11699·0	130·79	+0·1838	NS	51	73·922	39·049	365·20	3515·7	9612·6	73·950	0·03799	NS	Croll (1933).
	F.	58	140·86	35·069	4826·6	12057·0	14274·0	142·53	0·3381	xx	58	77·845	36·069	2751·1	5880·6	14274·0	78·603	0·19273	x	
Pold Village ..	M.	52	123·65	34·250	−247·50	17806·0	9923·8	123·51	−0·02494	NS	52	69·135	35·596	−3440·7	5411·1	8534·5	67·358	−0·4032	xxx	Croll (1933).
	F.	66	129·02	30·924	1207·6	10386·0	13110·0	129·86	0·09211	NS	66	72·803	30·924	−393·49	5331·4	13110·0	72·581	−0·03001	NS	
Hammond Island ..	M.	20	131·75	33·350	2455·2	2788·8	7200·6	134·02	0·3410	x	20	74·750	36·850	1491·8	1098·8	5786·5	75·563	0·2578	NS	Croll (1933).
	F.	26	136·55	31·654	219·62	4602·9	4955·4	136·72	0·04432	NS	26	76·731	33·961	249·23	1672·1	4018·5	77·255	0·06691	NS	
St. Pauls	M.	60	133·25	35·717	−492·25	9816·2	18805·0	133·14	−0·02618	NS	60	77·117	35·717	220·48	4951·2	18804·0	77·167	0·01173	NS	Croll (1933).
	F.	79	137·34	26·487	−827·65	17342·0	9865·0	136·21	−0·08390	NS	79	79·304	26·487	−1935·7	8211·7	9875·0	76·655	−0·1960	NS	
Mabuiag Island ..	M.	67	141·64	36·515	2283·4	12619·0	18730·0	142·07	0·1219	NS	67	83·433	36·515	1896·6	8510·4	18743·0	83·786	0·1012	NS	Croll (1933).
	F.	99	139·80	30·389	857·78	22596·0	24040·0	142·41	0·03568	NS	102	80·931	30·226	−278·92	11162·0	24310·0	80·810	−0·01147	NS	
Mapoon	M.	45	151·56	38·833	1106·7	11791·0	10450·0	151·68	0·1059	NS	46	84·130	39·630	265·22	5715·2	9315·2	84·149	0·02847	NS	Croll (1933).
	F.	77	142·53	28·357	5402·9	19956·0	14041·0	147·01	0·3848	x	77	80·065	28·357	1715·7	7249·7	1404·1	81·488	0·1222	NS	
Aurukun	M.	76	145·93	38·868	4384·2	18136·0	14772·0	146·26	0·2968	x	76	78·947	30·132	1639·5	7115·8	14772·0	80·043	0·1110	NS	Croll (1933).
	F.	82	147·38	31·268	2586·2	19786·0	15959·0	148·79	0·1620	NS	83	80·602	31·187	−44·34	7669·9	16004·0	80·578	−0·00277	NS	
Weipa	M.	59	142·97	34·839	1490·7	17431·0	18508·0	143·54	0·1104	NS	57	79·825	34·833	−596·67	6098·3	12743·0	79·583	−0·04682	NS	Croll (1933).
	F.	58	142·67	35·517	3482·3	20536·0	11489·0	144·03	0·3031	x	58	80·431	35·517	1424·6	9639·2	11489·0	80·986	0·1240	NS	
Mitchell River ..	M.	99	150·46	41·237	2486·8	22730·0	23833·0	150·32	0·1043	NS	100	84·900	40·980	−3495·2	10899·0	24489·0	85·040	−0·1427	x	Croll (1933).
	F.	127	153·07	33·185	9407·8	27802·0	28383·0	155·33	0·3814	xxx	127	81·417	33·185	3216·7	12345·0	28383·0	82·190	0·1133	NS	

[1] Σxy = corrected sum of products of pressure times age.
[2] Σy^2 = corrected sum of squares for pressure.
[3] Σx^2 = corrected sum of squares for age.
[4] a = value of regression line at 40 years.
[5] b = regression coefficient.
[6] P = significance of difference between b and 0.
NS = not significant.
[7] x = 0·05 < P < 0·01.
[8] xx = 0·01 < P < 0·001.
[9] xxx = 0·001 < P.

cases only a rest pause of one to two minutes was allowed, but their previous activity was not at all strenuous. Masters *et alii* (1952) consider that this kind of reading is of more value than true basal readings. The systolic pressures were taken by auscultation, supplemented at times by palpation, the diastolic by auscultation of the sudden muffling of the sounds. This latter was necessary to ensure uniformity among the different series. Variation in arm diameter is of some importance for the mean pressure, but does not affect the regression coefficients (Pickering *et alii*, 1952).

The ages of the aborigines are hard to discover. In Crosby and Kerr's and in my series help was obtained from an experienced anthropologist, from a dentist and from station records. In general they are accurate to about five years in adults. The other investigations mostly used station records or estimations. Croll's 1938 study comprised individuals of 12 years or over (personal communication); the remainder included those aged 10 years or over, except for the females of my 1956 Haast's Bluff series, in which five years was used as a lower limit.

The diets of the Central Australian groups have been described by Campbell (1939*a*, 1939*b*, 1939*c*) and others, but the quantitative intake depends mainly upon what is available at the time. Rough estimations of the diets were made by a number of the observers, who also observed the natives' physical condition.

The statistical methods used are described in the appendix. Each separate group of results, for males or females, was fitted with a linear regression line. The value for this line at 40 years was called a; it gives a slightly better representation of the group than does the mean. The slope of the line is indicated by b (Table I). The individual results are also grouped according to the extent of adoption of European ways, and whether the subjects came from Central Australia or from Queensland (Tables II and III).

RESULTS.

All Groups Combined.

The systolic pressures at 40 years (a values) were 136·81 millimetres of mercury for men, 140·15 for women, and 138·40 for both together. The difference between the sexes was highly significant. The increases with age (b values) were 0·17969, 0·26453 and 0·22297 millimetres of mercury per year respectively. The difference between the sexes was not significant. The a figures for the diastolic pressures were 80·081, 79·875 and 79·980 millimetres of mercury, while the b values were 0·080368, 0·087336 and 0·083928 millimetres of mercury for the same persons. The difference between the sexes was not significant. The grand variance for systolic pressure was 228·331 millimetres of mercury on 1929 degrees of freedom; that for diastolic pressure was 100·506 millimetres of mercury on 1934 degrees of freedom (this was the variance obtained by removing the effect of the linear regressions).

Comparisons Among Aboriginal Groups.

Tables II and III give comparisons among aboriginal groups living in the settlements marked on the map in Figure I.

A. Central Australia—Native Conditions.

These people had not been influenced by Europeans. Their diet at the time would have been principally plants and fat-poor animals. The authors (Hicks *et alii*, 1934) remark on the drought conditions, and on the poor physique of the natives—except for some Pintubis. Such factors may have reduced the pressures below the levels they would otherwise have reached, but similar interludes must occur fairly frequently with an equally frequent effect upon the pressures.

B. Central Australia—Partly Europeanized Conditions.

These natives fall into two sub-groups. First, those who visit the settlements only very occasionally for short periods. Secondly, those who live around the settlements for most of the time and more or less continuously enjoy

TABLE II.
Grouped Data.

Group.	Individual Areas.	Sex.	Systolic Pressure.					Diastolic Pressure.					
			$\bar{a}$	P[1]	Standard Error.	$\bar{b}$	P	$\bar{a}$	P	Standard Error.	$\bar{b}$	P	Standard Error.
A. Central Australia—primitive.	Mt. Leibig, Cockatoo Creek.	M.	109·12	NS	2·086	0·3163	NS	74·966	NS	1·391	0·2984	NS	0·07941
		F.	106·03	—	5·471	0·4110	—	67·503	—	3·752	−0·1085	—	0·2016
		Total	108·73 (NS)[2]	NS	1·949	0·3301 (NS)	NS	74·068 (NS)	NS	1·305	0·2437 (NS)	NS	0·07389
B. Central Australia—semi-civilized.	Haast's Bluff, 1956. Haast's Bluff, 1957. Yuendumu, 1951. Yuendumu, 1956.	M.	118·53	NS	1·704	0·03393	NS	79·313	x	1·345	0·01005	NS	0·06020
		F.	110·46	xxx	2·140	0·02395	NS	76·080	xxx	1·527	0·04506	xx	0·07242
		Total	114·90 (xx)	xxx	1·384	0·02921 (NS)	NS	77·853 (NS)	xxx	1·013	0·02486 (NS)	x	0·04629
C. Central Australia—semi-civilized.	Bungalow.	M.	131·41	—	3·484	0·3979	—	88·723	—	2·538	0·2895	—	0·1626
		F.	115·86	—	3·561	0·2934	—	75·310	—	2·300	0·04018	—	0·1408
		Total	123·80 (xx)	—	2·491	0·3404 (NS)	—	81·357 (xxx)	—	1·704	0·1546 (NS)	—	0·1102
D. Carpentaria	Mapoon, Aurukun, Weipa, Mitchell River.	M.	148·09	x	0·9414	0·1513	NS	82·730	xx	0·6603	−0·03567	NS	0·04049
		F.	150·18	xxx	0·9808	0·2990	NS	81·471	NS	0·6193	0·09027	NS	0·03791
		Total	149·12 (NS)	xxx	0·6757	0·2292 (NS)	NS	82·078 (NS)	xx	0·4506	0·03149 (x)	NS	0·02767
E. East Queensland.	Yarrabah, Mona Mona, Lockhart River.	M.	141·01	xx	1·161	0·4419	NS	82·350	NS	0·7369	0·2732	xx	0·04589
		F.	141·76	xxx	1·105	0·4773	x	82·423	NS	0·7288	0·1862	NS	0·03899
		Total	141·39 (NS)	xxx	0·8181	0·4622 (NS)	x	82·387 (NS)	NS	0·5182	0·2226 (NS)	xx	0·02971
F. Torres Strait.	Cowrl Creek, Pold Village, Hammond Island, Mabuiag Island, St. Pauls.	M.	133·33	xxx	1·088	0·02785	NS	76·228	xxx	0·6647	0·008674	xxx	0·04043
		F.	138·41	xxx	1·076	0·09486	NS	77·674	xxx	0·6976	0·007500	x	0·03914
		Total	135·82 (xxx)	xxx	0·7682	0·06182 (NS)	NS	76·938 (NS)	xxx	0·5094	0·006070 (NS)	xx	0·02813

[1] P stands for the significance of the tests for non-homogeneity between the individuals composing the group.
[2] Symbols after the total $\bar{a}$ and $\bar{b}$ values stand for the significance of the differences between the sexes.

TABLE III.
Significance of Differences between Groups.[1]

Group I.	Group II.	Sex.	Systolic Pressure.		Diastolic Pressure.	
			$\bar{a}$ (I *minus* II).	$\bar{b}$ (I *minus* II).	$\bar{a}$ (I *minus* II).	$\bar{b}$ (I *minus* II).
B. Central Australia—semi-civilized.	A. Central Australia—primitive.	M. ..	9·41 (xxx)	−0·282 (NS)	4·35 (x)	−0·288 (xx)
		F. ..	4·43 (NS)	−0·386 (NS)	8·58 (x)	0·154 (NS)
		Total ..	6·17 (xx)	−0·301 (x)	3·78 (x)	−0·219 (x)
C. Bungalow.	B. Central Australia — semi-civilized.	M. ..	12·87 (xxx)	0·364 (NS)	9·41 (xxx)	−0·279 (NS)
		F. ..	5·39 (NS)	0·269 (NS)	−0·77 (NS)	0·005 (NS)
		Total ..	8·90 (xx)	0·311(NS)	3·50 (NS)	−0·130 (NS)
C. Bungalow.	D. Central Australia—primitive.	M. ..	22·28 (xxx)	0·082 (NS)	13·76 (xxx)	−0·009 (NS)
		F. ..	9·83 (NS)	−0·118 (NS)	7·81 (NS)	0·149 (NS)
		Total ..	15·07 (xxx)	0·010 (NS)	7·29 (xxx)	−0·189 (NS)
D. Carpentaria—primitive.	E. East Queensland — semi-civilized.	M. ..	7·09 (xxx)	−0·291 (xx)	0·38 (NS)	−0·309 (xxx)
		F. ..	8·31 (xxx)	−0·178 (x)	−0·95 (NS)	−0·096 (NS)
		Total ..	7·72 (xxx)	−0·233 (xxx)	0·21 (NS)	−0·191 (xxx)
E. East Queensland—semi-civilized.	F. Torres Strait—semicivilized.	M. ..	7·67 (xxx)	0·414 (xxx)	6·12 (xxx)	0·264 (xxx)
		F. ..	3·35 (x)	0·382 (xxx)	4·95 (xxx)	0·179 (xx)
		Total ..	5·57 (xxx)	0·401 (xxx)	5·45 (xxx)	0·216 (xxx)
D. Carpentaria—primitive.	F. Torres Strait—semicivilized.	M. ..	14·76 (xxx)	0·124 (NS)	6·50 (xxx)	−0·044 (NS)
		F. ..	11·76 (xxx)	0·104 (NS)	3·80 (xxx)	0·083 (NS)
		Total ..	12·30 (xxx)	0·168 (xx)	5·14 (xxx)	0·023 (NS)
D. Carpentaria—primitive.	A. Central Australia—primitive.	M. ..	38·97 (xxx)	−0·165 (NS)	7·76 (xxx)	−0·334 (xxx)
		F. ..	44·14 (xxx)	−0·112 (NS)	13·97 (xxx)	0·199 (NS)
		Total ..	40·39 (xxx)	−0·101 (NS)	8·01 (xxx)	−0·212 (xx)
F. Torres Strait — semi-civilized.	C. Bungalow. ..	M. ..	1·93 (NS)	−0·370 (NS)	−12·49 (xxx)	−0·281 (NS)
		F. ..	12·55 (xxx)	−0·198 (NS)	2·36 (NS)	−0·033 (NS)
		Total ..	11·02 (xxx)	−0·279 (NS)	−4·42 (x)	−0·147 (xx)

[1] Where all differences are of Group I *minus* Group II, their significances are shown after the differences.

the Government supplements of meat, flour, sugar, vegetables, fruit and a little butter or dripping, and a few other supplies from the store. The former group comprises 28 Pintubis who had just come in from the Western Desert. They were examined by myself in 1957. They were closely similar to the natives described by Hicks *et*

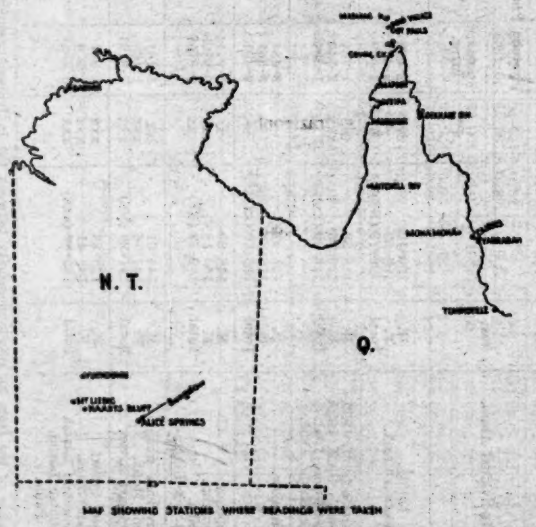

FIGURE I.
Map showing settlements where natives were investigated.

alii, but appeared to have experienced a good season. The remainder were examined at Yuendumu in 1951 (Crosby and Kerr, personal communication) and in 1956 (Poidevin, personal communication) and at Haast's Bluff in 1956 by myself. There were no significant differences between these two sub-groups. The whole group's systolic and diastolic a values are greater than those of group A, but some of their regression coefficients (b values) are smaller. There is quite a difference between the figures of Crosby and Kerr and those of Poidevin, both on Ngalias (Wailbrais) at Yuendumu. The reason for this is not apparent.

C. Central Australia—Bungalow.

This is a special case. The group lives at a settlement, "The Bungalow", just outside Alice Springs, and supplies labour for the town. Also included here are the pressures of some healthy native visitors to the hospital, who came from stations etc., and were at a similar level of civilization. The men live almost entirely on a European diet—either from the settlement or bought in the town. The women partly do so too, but included are a number of women, native to the area, who also use native foods to some extent. The settlement comprises a mixture drawn from about seven surrounding tribes. The men's systolic and diastolic a values are very significantly greater than those of the less Europeanized groups, A and B. The women's pressures were increased, but just not significantly so. None of the b values is significantly different from groups A and B.

D. Gulf of Carpentaria—Native Conditions.

When examined in 1938, these natives had had little contact with civilization until some 15 years before (Croll, personal communication). Their conditions were still very primitive; they had mostly native diet with no butter or dripping. But the land is much more fertile and their food intake was probably greater than that of the Central Australians. Also they were near the sea, so that fish and dugong were added to the usual native diet (dugong oil is a good source of animal fat), and some beef was available from Government sources. Their systolic a values are very high (148 to 150 millimetres of mercury), while those of their diastolic pressures (81 to 83 millimetres of mercury) are also greater than those of the corresponding group in Central Australia.

E. East Queensland—Partly Europeanized Conditions.

These aborigines had been in contact with Europeans for 50 years when observed. Their diet included dugong, fish, beef, milk, butter and dripping. (Mona Mona was vegetarian—but only nominally so according to Croll.) Their native foods were added to by the Government. They systolic a values are lower than those recorded around the Gulf of Carpentaria, but higher than those of Torres

Strait islanders. This also holds for the diastolic pressures. However, this group's pressures increase more with age than do those of groups D and F.

F. Torres Strait Islanders—Partly Europeanized Conditions.

These lived on islands just north of Cape York Peninsula and on the top of the peninsula itself. They are of mainly Australian aboriginal descent, though there is a slight Melanesian admixture. Contact with European civilization had occurred for 50 years. Their diet was mainly European, with some butter and dripping, but they also used native foods with fish and dugong oil. Their systolic and diastolic a values are considerably lower than those around the Gulf of Carpentaria and in east Queensland.

General.

Summarizing the results, one may state broadly that the Central Australian natives have low pristine systolic pressures that rise with increasing European contact; Queensland's natives have high pristine values that fall with Europeanization. The diastolic pressures in general follow this pattern, though not so markedly. The regression coefficients (b values) seem to vary independently of the levels at 40 years (a values).

Comparison with Europeans.

It is rather hard to decide which series of figures from Europeans to use as a control. To my knowledge there have been no series of measurements on Europeans living in Australia. There have been a number done in Europe, America and Great Britain (Table IV). However, some of these were done on individuals who had applied for insurance, or who had even been accepted for it. Robinson and Brucer's (1939) results are the best known of this group. The values used here are from their full series, not just those less than 140/90 millimetres of mercury, which they arbitrarily set as the upper limit of "normality" (Treloar, 1940; Pickering, 1955). Even so their figures are probably too low to represent the normal—in the sense of usual—pressures in the general population, since their subjects had been accepted for insurance. Russek *et alii* (1946) used men aged 40 to 90 years. They also used the statistically dubious device of ignoring those pressures they thought were abnormal, by cutting a continuous distribution at an arbitrary point. Again the results of their total series are used. Gover (1948) studied families of low income. Masters *et alii* (1952) used mostly European people applying for work in many different occupations. This must have implied that the subjects felt fairly fit. In contrast to those four studies in the U.S.A., Hamilton *et alii* (1954) in Great Britain used patients attending out-patients' clinics, who were unlikely to be selectively associated with hypertension. Bøe *et alii* (1957) studied almost the entire city of Bergen. For some unknown reason, the two groups into which their data were arbitrarily divided were not identical, and are shown separately. In Table IV the mean pressures at 40 years of age and the regression coefficients are shown. These were given, could be calculated, or were estimated by eye from the graphs. Where given, the standard errors (S.E.) are shown. In all cases, except Russek *et alii* (1946), the age distributions were similar to those of the aborigines. The series of Hamilton *et alii* (1954) and of Bøe *et alii* (1957) seem the most representative of the general European population. Their statistics were easy to use and are probably the best for comparison.

Comparing the values of Tables II and IV, it will be seen that the systolic a values of Central Australian natives are lower and those of Queenslanders higher than those in most European series. With increasing Europeanization, the natives' values tend towards those of Europeans. In general, the b values for systolic pressures of all natives are less than Europeans—in some cases markedly so. The diastolic a values show no very marked differences, except that those for pristine Central Australians and Torres Strait islanders are slightly low, and those for Europeanized Central Australians slightly high. The increases with age are again lower for aborigines.

Discussion.

Our knowledge of the conditions of life of the aborigines is far less extensive even than our knowledge of those of Europeans. So it would be rash to attempt any very detailed interpretation of these results. Still, it is possible to give some indication of their relation to the observations of others.

Differences in the Levels of Blood Pressure.

It is well known that environment has a great influence on blood pressure, e.g. students coming to the U.S.A. increase their pressures (Szent-Györgyi, 1956); American Negroes have much higher pressures, which increase more with age, than African Negroes, according to studies summarized by Pickering (1955). But opinions differ about the causes for this: differences in total calorie, fat, salt or protein intake, psychic factors and the prevalence of diseases have all been blamed.

Regarding the aborigines, it is highly probable that those living under primitive conditions in Central Australia were on a far poorer diet than were those in Queensland. The former have little fat (Schwartz *et alii*, 1957), whereas the latter have more (Croll, personal communication). With increasing contact with European

TABLE IV.

European Figures by Other Investigators.

Observer.	Sex.	Systolic Pressure.				Diastolic Pressure.			
		a	Standard Error.	b	Standard Error.	a	Standard Error.	b	Standard Error.
Robinson and Brucer (1939) ..	M.	120·8	0·197	0·203	0·0103	74·2	0·122	0·198	0·0103
	F.	115·8	0·191	0·403	0·0179	69·8	0·204	0·418	0·0179
Russek *et alii* (1946)	M.	133G[1]	0·57	0·45G	—	85G	0·37	0·01G	—
Gover (1948)	M.	137G	0·64	0·57G	—	82G	0·41	0·33G	—
	F.	141G	0·94	1·20G	—	85G	0·46	0·43G	—
Masters *et alii* (1950)	M.	128·2	0·173	0·42G	—	80·9	0·175	0·20G	—
	F.	125·8	0·116	0·65G	—	78·9	0·116	0·30G	—
Hamilton *et alii* (1954)	M.	129·8	1·182	0·758	0·0602	77·7	0·620	0·353	0·0359
	F.	133·7	1·182	1·143	0·0602	80·4	0·620	0·464	0·0359
Bøe *et alii* (1957), Group I ..	M.	143G	0·42	0·64G	—	80G	0·26	0·29G	—
	F.	141G	0·35	1·00G	—	81G	0·21	0·46G	—
Bøe *et alii* (1957), Group II ..	M.	132G	0·53	0·50G	—	82G	0·42	0·29G	—
	F.	131G	0·46	0·86G	—	81G	0·36	0·44G	—

[1] G after a figure means it was estimated, by eye, from a graph.

civilization, the amount of fat and the total caloric intake rise for the Central Australians. The Bungalow men visited the town more than the women, and would have taken the greatest share of the available fat. This possibly accounts for the women's pressures being lower than the men's. The effect of European civilization on the Queenslanders is harder to determine. Under native conditions these probably have a high caloric intake with a fairly high fat intake due to various fat-rich foods, of which dugong oil is one. When they are given the Government supplement which is principally flour and sugar, their intake of native fats is likely to fall. Thus they may eat less in spite of receiving small amounts of butter and dripping. Variations in salt intake and the effects of dehydration may be of some importance. At present there are few data on these topics, but there is a suggestion that they may be related to the raised hæmoglobin value of the pristine natives (Casley-Smith, 1958). The influence of past disease and psychic factors is very difficult to assess.

It is possible that genetical differences are of some importance. Pickering (1955) estimates that inheritance is roughly equal to environment in producing hypertension; probably this is also true in the lower ranges of pressure. There is little known of aboriginal genetics, but what there is (Abbie, 1947, 1951; Simmons *et alii*, 1954) suggests a high degree of homogeneity. Thus it is likely that the observed differences are environmental rather than genetic in origin.

"Normal" Values.

Definitions of and values ascribed to "normal" blood pressure have varied very much. Some (Masters *et alii*, 1952) derive their values from the whole population, and use a purely statistical definition of the limits of normality. Others (Robinson and Brucer, 1939, and many others) use various methods, including life tables, to arrive at a figure above which most people experience some disabilities. Still others consider hypertension as merely the upper ranges of a quantity whose effects gradually increase without any sharp division (Pickering, 1955). Thus some use "normal" for the pressure people actually possess, others use it for that which they ought to have. It is clear that among genetically similar aborigines some groups have mean pressures lower than European means, others higher. The increase with age in all aborigines is generally less than in Europeans.

Type of Difference in Pressure.

Both Queenslanders and Central Australians have diastolic pressures approximating to those of Europeans, but the Queenslanders' systolic pressures are greater than, and the Central Australians' less than, those of Europeans. Thus the Queenslanders' pulse pressure is greater than that of Central Australians, though Europeanization brings them both to about the European pulse pressure. This difference corresponds to "systolic hypertension", which Pickering (1955) considers due simply to loss of elasticity of the great vessels. Others (Wiggers, 1937; Zeman and Schwartz, 1948) emphasize that there may be associated increased peripheral resistance too. They state that a normal diastolic pressure, in the presence of a raised systolic pressure, does not exclude essential hypertension. Be that as it may, this increase in pulse pressure suggests a decrease in elasticity of the great vessels in the Queensland groups for some reason not immediately obvious.

Relationship to Atherosclerosis.

Under primitive conditions, the concurrence of low blood pressures, low incidence of atheroma, low serum cholesterol levels and low fat diets has been noted (Kean and Hammill, 1949), e.g. in African natives (Donnison, 1929; Walker and Arvidson, 1954; Bronte-Stewart *et alii*, 1955; Mann, *et alii*, 1955). However, urbanized natives have higher blood pressures, a large amount of fat in their diet, higher cholesterol levels and more evidence of atheroma (Ordman, 1948; Walker and Arvidson, 1954). Some criticism has been levelled at parts of this work, e.g. where the amount of atheroma has been estimated by coronary thrombosis, since a high fat diet also reduces the fibrinolytic factors in the blood (Gillman *et alii*, 1957). But the pristine Central Australian natives also have a low fat diet, low serum cholesterol levels, a low incidence of atheroma (Schwartz *et alii*, 1957; Schwartz and Casley-Smith, 1958*a*) and low blood pressures. Of atheroma little is known, but all the others increase with urbanization. The serum mucoprotein levels—reflecting ground substance breakdown—also follow this pattern (Schwartz and Casley-Smith, 1958*b*). The relationship between these various factors is mostly unknown, though variation in dietary fat has been postulated as the primary cause of the differences.

The influence of blood pressure on atheroma and *vice versa* is not clear. Many pathologists hold that hypertension causes atheroma to be more extensive and severe. This is also true in animal experiments (Pickering, 1955). However, many people with much atheroma are normotensive; others with little are hypertensive (Zeman and Schwartz, 1948). The amount of atheroma does not correlate well with the degree of hypertension (Davis and Klainer, 1940), especially in certain vessels. Thus hypertension is one, but not the only, factor determining the presence and amount of atheroma. The difference in blood pressure between groups of aborigines seems to offer an opportunity for extending our knowledge of these relations. At the moment we need information on the amount of atheroma and on the serum cholesterol and mucoprotein levels in the Queensland group.

Summary.

1. The blood pressures of about 2000 aborigines, living under various conditions, are reported. The recording was done by a number of different observers.

2. The pressures, especially the systolic, in Central Australia were lower, and those in Queensland markedly higher, than those in comparable Europeans. In both groups, pressures rose more slowly with age than in the Europeans.

3. The Central Australian pressures increased with increasing European contact; the Queensland pressures diminished on such contact.

Acknowledgements.

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Thanks are due also to the Hon. Paul Hasluck, Minister for Territories, to His Honour the Administrator of the Northern Territory, and to the Director of Native Welfare for affording access to the native settlements. To these, and to the managers of the various settlements, I am very much indebted.

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APPENDIX.

Statistical Analysis.

The observations on each sample of natives were analysed separately. Linear regression lines were fitted to both sexes of each sample. It is possible that higher order regressions would have fitted significantly more accurately, but to use these would have introduced difficulties in analysis. The age ranges are similar, except for Nye's (1937) sample; and the curves of most workers are roughly similar, with positive second derivatives. So linear regressions gave all the information required in this instance (compare Pickering, 1955). These linear regression coefficients, b, are shown in Table I, as well as the mean pressures, a, of each group and the value of the regression line at the age of 40 years, α. This is obtained from the regression equation, $y=a+b(x-\bar{x})$, by letting $x=40$, where $y_{40}=\alpha=a+b(40-\bar{x})$, where y represents the pressure, x the age, and $\bar{x}$ the mean age. The new regression equation is: $y=\alpha+b(x-40)$. This value gives a better representation of the level of blood pressure in the sample than does the mean a $(=\bar{y})$; the latter takes no account of the mean age of the sample. However, α has a greater error than a since it is the sum of a and a second factor, both subject to errors in estimation. If s^2 is the estimate of the variance of the sample and n is the number of individuals, the variance of a is $\frac{s^2}{n}$, and that of α is: $v=s^2\left\{\frac{1}{n}+\frac{(40-\bar{x})^2}{\Sigma(x-\bar{x})^2}\right\}$ (Fisher, 1950). Let $\frac{1}{v}=w$. If s^2 is the same for all α values, then w is inversely proportional to the variance of a sample's α; it is the appropriate factor to use for weighting the α values when various samples are combined into one group. Thus $\bar{\alpha}=\frac{\Sigma w_1\alpha_1}{\Sigma w_1}$, summing over individual α_1's etc. Similarly, with the b values, the variance of b is $\frac{s^2}{\Sigma x_1^2}$ and of $\bar{b}=\frac{\Sigma x_1^2 b_1}{\Sigma x_1^2}$.

The samples were grouped by sexes and both together. The individual variances of systolic pressures were similar and were best combined. This was also done with those of the diastolic pressure. (Nye's results could not be used in these estimations as the variances of the pressures were not given.) The "F tests" show that all these large groups are non-homogeneous; they can be split into smaller groups for comparison. To make the comparisons mean more, the samples are grouped according to geographical distribution and level of civilization. These are shown in Table II, where the homogeneity or otherwise of these minor groups is shown. In those that are non-homogeneous, the best estimate of the variance of $\bar{\alpha}$ or $\bar{b}$ is not simply $\frac{s^2}{\Sigma w_1}$ or $\frac{s^2}{\Sigma x_1^2}$. Allowance has to be made for the significant difference of the individual α and b values from the group means, i.e. from $\bar{\alpha}$ and $\bar{b}$. This is done by using $\left\{\frac{s^2}{\Sigma w_1}+\frac{\Sigma d_1^2 w_1}{(\Sigma w_1)^2}\right\}$ as the variance, where d_1 is the difference between the individual α_1 or b_1, and $\bar{\alpha}$ or $\bar{b}$. This process is only really valid if all the separate elements in each sample fall approximately into a normal distribution when grouped together. It was held that the large standard deviations of the samples and the relatively small differences between their α and b values made this approximation reasonable. The "t tests" on the differences between the different groups are shown in Table IV. It should be noted that large differences in the b values may be introduced by differences in observers' methods of estimation of age, so not too much stress should be laid on comparisons between different workers' groups.

Reports of Cases.

PYODERMA GANGRENOSUM CONTROLLED BY CORTISONE: REPORT OF A CASE.[1]

By R. F. A. BECKE AND T. F. ROSE,
The Royal North Shore Hospital, Sydney.

IN 1909, W. H. Luckett described a large phagedenic ulcer of the skin of the abdomen following the squeezing of a pimple with the finger nail six days previously. The ulcer

[1] Read at the tenth annual meeting of the Dermatological Association of Australia, Queensland, July, 1958.

spread progressively with a wide, red margin shading into surrounding normal skin until it reached a size of 10 in. by 5 in. Inside the outer red margin was a discoloured greyish zone, and more centrally, dark gangrenous tissue with the underlying ulcer base revealed as greyish-red granulations bathed in purulent exudate. The lesion was painful, and the patient febrile. *Staphylococcus aureus* was cultured. Prompt recovery with speedy healing of the ulcer followed total surgical ablation with the cautery. The excision included healthy skin beyond the red margin.

In 1924, T. S. Cullen described a progressively enlarging ulcer of the abdominal wall following drainage of an appendiceal abscess. Since these two early descriptions, the condition, and clinically similar conditions, have been recorded under such names as pyoderma (ecthyma) gangrenosum, dermatitis gangrenosa, phagedena geometrica, symbiotic gangrene and progressive bacterial synergistic gangrene. It is different from the hæmolytic streptococcus gangrene described by Meleney in 1924. In the last condition the constitutional symptoms are acute and severe, with an erysipelas-like picture and overwhelming septicæmia and toxæmia, although the ulcers in the two conditions are indistinguishable clinically.

Brewer and Meleney (1926) suggested the infective ætiology of this type of ulceration. They were able to isolate a micro-aerophilic, non-hæmolytic *Streptococcus* and a hæmolytic *Staph. aureus* from a gangrenous ulcer of the abdominal wall, which followed the drainage of an appendiceal abscess. They succeeded in reproducing the lesion experimentally in guinea-pigs and rabbits by the hypodermic injection of a mixture of the two organisms, but could not reproduce it by the injection of either organism alone. Meleney (1931) confirmed those observations, but there have been many unsuccessful attempts at isolation of the organisms. This lack of success may be attributable to the use of antibiotics before culture, or to a severe inflammatory reaction, causing early destruction of the organisms, or even to inadequate cultural procedures.

Organisms other than the two usual synergistic cocci are described as being associated with this ulcerative process—e.g., *Pseudomonas æruginosa* (*Bacillus pyocyaneus*), *Proteus vulgaris* and *Escherichia coli*.

The lesions have developed following such diverse events as contusions, abrasions, lacerations, insect bites, boils, gunshot wounds and surgical operations. They sometimes occur in association with ulcerative colitis, and one case has been described in the course of periarteritis nodosa. Recent investigations suggest a relationship between pyoderma gangrenosum and disturbances of blood proteins in the direction of hypogammaglobulinæmia.

Clinically, the appearance of the lesions is characteristic, and there appears to be no essential difference in nature between any of the ulcers described under such varying names. The ulcerative process affects the skin and the subcutaneous tissue, although it may involve deeper structures by direct extension, and is more superficial than the destruction produced *en masse* by true gangrene (death of tissue). Three to seven days following a contusion abrasion or surgical wound the skin becomes inflamed and swollen; alternatively a blister may develop without known injury. In either case ulceration develops within 48 hours. The ulcer spreads peripherally with considerable rapidity its advancing edge being bright red and up to one and a half inches in width. Within this margin is a raised purplish bullous and undermined zone, merging centrally with a dark, escharotic, gangrenous area. The shedding of the gangrenous tissue reveals the centre of the ulcer, deep, with greyish-red granulation tissue and considerable exudate. Tiny greyish islets of epithelium are present on the surface granulations, and from these the skin and its appendages are eventually regenerated. The lesion may become very large, and multiple discrete areas may develop. Deep lesions penetrate through the fasciæ and may threaten to erode large blood vessels. Tendons may become exposed. In prolonged cases delayed healing has caused grave toxicity and anæmia. When healing commences there is rapid epithelialization from the abundant focal epithelial remnants. The scar is characteristically tough, greyish-white and parchment-like, following the serpiginous contours of the ulcerated area.

Common methods of treatment include surgical excision with or without grafting, cautery excision (Luckett, 1909), diathermy excision and grafting (Beard, 1956), long-continued high dosage with antibiotics and the injection of gammaglobulin. Recently, steroid hormones have been used successfully (Wright and Greco, 1956).

The following case is presented as one controlled by cortisone. None of the organisms found were acceptable as ætiological types, and the ulceration was associated with hypogammaglobulinæmia. There were no symptoms or signs suggesting ulcerative colitis.

Clinical Record.

The patient, a married woman, aged 32 years, a housewife and a waitress, was admitted to hospital on February 4, 1958. Eighteen days previously she had slightly lacerated her left shin on a metal doll's pram. The wound bled a little, and five days later became swollen, bluish and painful. Ulceration occurred in the next two days. The ulcer developed a wide red margin and spread in an irregular centrifugal fashion. Pain was intermittent and throbbing but not severe. There was some numbness of the leg for five days before her admission to hospital. At this stage she was treated with one penicillin injection, with "Chloromycetin" capsules for three days and finally, erythromycin capsules for a further two to three days. She had noticed shivering attacks and feverishness in the last three days before admission to hospital.

Her previous medical history included total hysterectomy for ovarian cyst at the age of 30 years, appendicectomy at the age of 12 years, and traumatic ulcer of the ankle at the age of 10 years, which healed quickly. She had always had "good healing flesh". There was no family history of any skin or allergic disease, and no personal history of gastro-intestinal disorders.

Examination revealed a young, healthy woman, well nourished, and not distressed. A large ulcer was present on the left shin, midway between the knee and ankle and almost encircling the calf at one point. The appearance of the ulcer was typical of pyoderma gangrenosum, with deep penetration, revealing a greyish-red sloughy base, and a dark gangrenous zone merging with a raised bluish bullous zone about half an inch wide. The most peripheral zone was red and œdematous, and was one inch wide. There was no lymphangitis, and no lymphadenitis. Her temperature was 103·4° F., pulse-rate 100 per minute, and blood pressure, 125/80 mm. of mercury. There was no evidence of peripheral vascular disorder, and no evidence of disease of the nervous or alimentary systems. The urine was normal, and the hæmoglobin value was 12·6 grammes per 100 ml. The white cell count was 18,200 per c.mm., showing neutrophil leucocytosis, and the random blood sugar level was 104 mgm. per 100 ml. Examination of the exudate from necrotic zones of the ulcer showed small numbers of gram-positive cocci in pairs. Attempts at aerobic and anaerobic cultures produced no growth. The ulcer continued to spread up and down the limb and posteriorly, eventually covering the greater part of the front of the leg (Figure I). At this stage diathermy excision was considered, but it was decided to try steroid hormone therapy. The spread of the ulcer was arrested 11 days after the patient's admission to hospital, and 36 hours after the commencement of cortisone given orally. The temperature, which had varied between 103° F. and 100° F., subsided rapidly. When the cortisone dosage was reduced to 50 mgm. twice a day five days later, the temperature rose again and healing ceased. ACTH was then given intravenously, together with the cortisone given orally. Two days later the temperature was normal again, with the ulcer again healing. At this stage 5 c.cm. of gamma globulin was given by intramuscular injection on three occasions over seven days, after electrophoresis had revealed the reduced level of this protein fraction.

Six weeks after her admission to hospital all treatment except local therapy was discontinued. When she was discharged two months after admission the ulcer had almost healed, there being two or three small circular areas remaining open (Figure II).

Investigations.

Frequent blood examinations revealed a satisfactory state of red and white cells. There was no significant anæmia. The number of the white cells varied between 21,500 and 8800 per c.mm., the constant finding being neutrophil leucocytosis. X-ray examinations of the chest and leg gave normal findings, the random blood sugar level was 104 mgm. per 100 ml., and the Mantoux test gave a negative result. Examination of tissue fluid by dark ground illumination showed no spirochætes; the complement fixation test gave a negative finding. The guinea-pig inoculation test showed no acid-fast bacilli after 70 days. Attempts at blood culture repeatedly produced no growth. Attempts at aerobic and anaerobic cultures taken from the spreading red edge (and adjacent normal skin) in the form of blocks of tissue persistently produced no growth for significant organisms. No fungi were revealed on attempts at culture.

FIGURE I.
The ulcer fully developed. Islets of epithelium are visible as greyish patches.

Examination of the serum proteins (March 4) gave the following findings. In the Biuret reaction, the total protein level was 5·7 grammes per 100 ml., albumin, 3·9 grammes per 100 ml., globulin, 1·8 grammes per 100 ml. Both the thymol turbidity and the zinc sulphate turbidity were 0·4 unit. The electrophoretic pattern was as follows: albumin, normal; alpha-1 globulin, normal; alpha-2 globulin, greatly increased; beta globulin, increased; gamma globulin, very much decreased.

Re-examination of serum proteins on March 21 after three 5 c.cm. doses of gamma globulin gave the following findings. The total protein level was 5·9 grammes per 100 ml., albumin, 3·3 grammes per 100 ml., globulin, 2·6 grammes per 100 ml., thymol turbidity, 0·3 unit, and zinc sulphate, 0·3 unit. The electrophoretic pattern was as follows: albumin, normal; alpha-1 globulin, normal; alpha-2 globulin, increased; beta globulin, increased; gamma globulin, very much decreased.

The report on the biopsy specimen on February 18 was as follows: "The inflammation is of a purulent non specific type. It has no tubercular pattern and there is no neoplasia. No organisms were seen in a gram stained slide or in one stained for fungus."

The patient's blood pressure and urine were normal throughout.

Treatment.

After the patient's admission to hospital, antibiotics were used initially, commencing with erythromycin, 250 mgm. every six hours, and penicillin, 500,000 units intramuscularly every eight hours, for seven days. The erythromycin was then suspended, and "Chloromycetin" commenced in doses of 250 mgm. every six hours. Seven days later the penicillin was suspended, and "Chloromycetin" was increased to 500 mgm. every eight hours, with a reduction later to 250 mgm. every six hours. The "Chloromycetin" was given for 28 days in all (total dosage, 33 grammes). Cortisone given orally, 100 mgm. every eight hours, was started nine days after admission. It was reduced after five days, and the temperature rose. Then ACTH, 100 units in a 5% dextrose saline solution, was given by continuous intravenous drip over 36 hours, and the temperature subsided again. Cortisone was continued in 50 mgm. doses twice a day for a further three weeks. The "Chloromycetin" treatment was used as a "cover" for the cortisone for most of the cortisone course. The total dosage of cortisone was five grammes. Eusol dressings and "Neotracin" ointment administered every two hours provided the best local treatment.

Pathogenesis.

The inability to demonstrate significant organisms in this and other cases, even in the early stages, suggests that primarily pyoderma gangrenosum is not a bacterial infection. The organisms usually reported in this disease could be expected to exhibit some sensitivity to the wide variety of antibiotics used, and the lack of response in this case to such agents is notable. There is no evidence of case-to-case infection. The response to steroid hormones suggests that the real basis of pyoderma gangrenosum is a necrotizing tissue process, the inflammatory phase of which is based on some antigen-antibody reaction, and is suppressed by cortisone, which depresses the antibody element revealed as hypogammaglobulinæmia. Ulcerative colitis, although often absent in these cases, can no longer be regarded as a bacterial infection. One may speculate whether a common reaction capable of affecting the skin or the bowel or both together is the explanation.

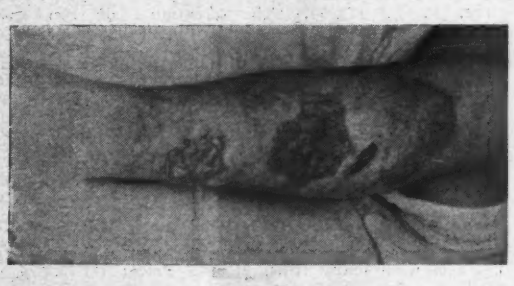

FIGURE II.
The ulcer largely healed. Residual open areas show regenerating epithelium.

Summary.

A case of pyoderma gangrenosum (symbiotic gangrene) treated with cortisone and antibiotics is described, with reference to some of the literature.

The ætiology of the condition is not known, but evidence of bacterial infection is wanting. A violent inflammatory tissue reaction to some unknown agent is suggested as the explanation, with cortisone acting as the depressor of the reaction.

There was no evidence of primary vascular changes or of malnutrition, and ulcerative colitis was not associated.

The reduction of the gamma globulin fraction of the serum proteins in this and other processes is worthy of further study.

Treatment with steroid hormones is recommended, although the beneficial role of surgery (with cautery or diathermy) is undoubted.

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Reviews.

Cardiovascular Disease. By David Scherf, M.D., F.A.C.P., and Linn J. Boyd, M.D., F.A.C.P.; Third Edition; 1958. *New York and London: Grune and Stratton.* 9½" x 6¼", pp. 846, with many illustrations. Price: $17.75.

THE third edition of this work maintains the high standard of its predecessors, and its value to student and physician lies in the emphasis laid on assessment of symptoms and significance of clinical signs. The authors have set out to present a text essentially on clinical cardio-vascular disease, and they have happily succeeded. They obviously intrude their own experience into many aspects of cardiology, and the reader has the impression of reading not orthodox cardiology, but conclusions and opinions reached by sound, down-to-earth observers. It is a refreshing text to the general physician, when so much current writing is weighted by excessive emphasis on laboratory methods, and the clinician is reassured that sound, accurate cardiology can be dispensed at a considerably less complicated level. The section on therapy is up to date; electrocardiography is wisely dealt with by the authors in a companion volume.

This book can be recommended as good reading and a sound approach to the practical problems of cardiological practice.

The Acute Abdomen. By William Requarth, M.D.; Second Edition; 1958. Chicago: The Year Book Publishers, Incorporated. Melbourne: Ramsay's Medical Books. 7¾" x 5¼", pp. 120, with 89 illustrations. Price, £3 11s. 6d.

THIS second edition of a book first published under the title of "The Diagnosis of Acute Abdominal Pain", has been enlarged by the inclusion of the principles of surgical treatment of the acute abdominal emergency.

There are two preliminary chapters on the examination of the abdomen and the differential diagnosis from the standpoint of location and type of pain. Then follow chapters on acute intestinal obstruction, diseases for which operation is imperative, diseases for which operation can be delayed and diseases for which operation is contraindicated or harmful. The three final chapters are on traumatic wounds of the abdomen, diagnosis of acute abdominal lesions in infants and the differential diagnosis of acute gastro-œsophageal hæmorrhage.

In the foreword it is stated that "in emergency conditions it is much more essential to make the correct decision to operate than it is to make an exact diagnosis". Whilst it may be admitted that an "exact" diagnosis is not always possible, the more accurate the diagnosis, the better will be the chances that the correct treatment will be ordered. It is putting the cart before the horse to classify acute abdominal diseases under treatment headings. Moreover, it tends to minimize the concept of disease as a continuous process—a surgeon must consider the whole "movie sequence" rather than make a quick decision on a single "frame". The author himself appears to have some misgivings, for his chapters are also grouped according to mode of onset. We think that had this been carried to its logical conclusion and the whole range of diseases classified in this way, the result would have been more satisfactory.

The separation of acute intestinal obstruction into a special chapter is on the premise that "this diagnosis should be evident after the initial examination of the patient". Most surgeons with experience of acute abdominal disease would be less dogmatic about their ability to isolate intestinal obstruction so easily.

The discussions of the various diseases are short, but clear and well written. Because of the method of classification, there is a considerable amount of overlap and repetition. The descriptions of the radiological findings are particularly good. The treatment paragraphs are necessarily brief, and the author has kept to his promise of describing principles only.

Despite the criticisms, this little book contains a wealth of information, and any young surgeon will learn a great deal from it. Its very unorthodoxy will stimulate his interest.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"The Central Nervous System and Behaviour: Transactions of the First Conference, February 23, 24, 25 and 26, 1958", edited by Mary A. B. Brazier, Ph.D.; 1959. Sponsored by The Josiah Macy, Jr. Foundation and The National Science Foundation. 9" x 6", pp. 450, with 168 illustrations. Price: $5.25.

The aim of this series of conferences is a thorough discussion and comparison of recent advances in this field in the Soviet Union and in the United States.

"Industrial Carcinogens", by R. E. Eckardt, M.D., Ph.D., F.A.C.P.; *Modern Monographs in Industrial Medicine*, Editor-in-Chief: Anthony J. Lanza, M.D.; Consulting Editor: Richard H. Orr, M.D.; 1959. New York and London: Grune & Stratton, Inc. 8½" x 5½", pp. 176, with 43 illustrations. Price: $6.50.

This volume is "intended for the beginning student of the subject".

"Recent Advances in Respiratory Tuberculosis", by Frederick Heaf, C.M.G., M.A., M.D., F.R.C.P., and N. Lloyd Rusby, M.A., D.M., F.R.C.P.; Fifth edition; 1959. London: J. & A. Churchill Limited. 8" x 5", pp. 292, with 6 plates and 14 text-figures. Price: 35s. (English).

The previous edition was published in 1948.

"A Short Practice of Surgery", by Hamilton Bailey, F.R.C.S. (Eng.), F.A.C.S., F.I.C.S., F.R.S.E., and McNeill Love, M.S. (Lond.), F.R.C.S. (Eng.), F.A.C.S., F.I.C.S., with chapters by John Charnley, F.R.C.S. (Eng.), William P. Cleland, M.R.C.P. (Lond.), F.R.C.S. (Eng.), and Geoffrey Knight, F.R.C.S. (Eng.); Eleventh edition; 1959. London: H. K. Lewis & Company Limited. 9¾" x 6¼", pp. 1401, with 1697 illustrations. Price: £4 4s. (English).

Fully revised and partly rewritten since the previous edition appeared in 1956.

"The Surgical Clinics of North America", December, 1958, Nationwide Number: "Soft Tissue Trauma", guest editor, James H. Forsee, M.D. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Limited. 8½" x 5½", pp. 299, with 54 illustrations. Price (six numbers): £8 2s. 6d. cloth binding; £6 15s. paper.

Contains a symposium on soft tissue trauma, with 19 papers by 27 authors.

"The Year Book of Radiology (1958-1959 Year Book Series)": "Radiologic Diagnosis", edited by John Floyd Holt, M.D., and Fred Jenner Hodges, M.D.; "Radiation Therapy", edited by Harold W. Jacox, M.D., and Morton M. Kligerman, M.D.; 1958. Chicago: The Year Book Publishers, Inc. Melbourne: W. Ramsay (Surgical) Limited. 9" x 5¾", pp. 448, with 335 illustrations. Price: £5 10s.

One of the Practical Medicine Series of Year Books.

The Medical Journal of Australia

SATURDAY, MAY 9, 1959.

MEDICINE AND ATOMIC ENERGY.

WHEN the atom bombs fell on Hiroshima and Nagasaki in 1945 and the war in the Pacific came to an abrupt end, it was soon asserted that the world would never be the same again, that we had passed into a new era. These statements may have seemed highly dramatic at the time, but it is fair to say that time has proved their truth. In most major world issues, and in many lesser facets of everyday life, our thoughts and decisions are constantly coloured by the effects of the release of atomic energy, whether for purposes of peace or of war.

Medicine is firmly involved in this situation. It is some consolation to realize that the peaceful uses of atomic energy in medicine—in research, clinical diagnosis and treatment—are of major and increasing importance. An indication of their scope may be obtained from an article by the British science writer, Ritchie Calder, published in this issue (see page 642), and we may hope that medicine has a great deal more to garner in this field that will be useful and constructive. At the same time we must think about the destructive effects, much as we may dislike doing so. The question of whether or not atomic weapons should be used in war is primarily political, and on this issue the proper role of the doctor as such is fulfilled when he has pointed out the biological and medical implications. It is most necessary, however, that he should know about what can happen if these weapons are used and think about what doctors should do in such a case.

Most people now know that the effects of an atomic explosion are produced by three components: blast, heat (with a blinding flash of light) and ionizing radiation. These effects have all been seen in grim reality, affecting human beings, as well as in tests under controlled conditions. They are depicted vividly in a human setting in two recently published Penguin books.[1,2] John Hersey's "Hiroshima" is of course not new. It originally appeared in 1946, having been written at literary white heat shortly after the devastation of the two Japanese cities by atom bombs. Now it has been reprinted as a companion volume to Ralph E. Lapp's account of "The Voyage of the Lucky Dragon". The two books are contrasting but complementary. Hersey plunges us swiftly and without superficial emotion into the centre of devastated Hiroshima. We are made to feel something of the impact of the sudden unexpected atomic attack and to see with crude vividness its immediate effects. Lapp, on the other hand, takes us with almost maddening leisure out on to the high seas with 23 Japanese fishermen on a fishing expedition in the tiny vessel *Fukuryu Maru* (*Lucky Dragon*). We share the insidious slowness of their contact with radioactive fall-out from the hydrogen bomb exploded on Bikini Atoll in March, 1954, and follow them through their subsequent experiences. In each case the story is centred about real people, and we are able to see the impact of an atomic explosion, immediate or remote, on men, women and children. This is the picture that we all need to see, for the explosion of an atomic weapon with destructive intent is before all else a human situation. Both authors write with sincerity and restraint; without obvious play on emotions or cheap journalistic tricks, they yet produce moving and absorbing stories. Style and development are wedded to subject matter with admirable skill. Read together these two books provide us not only with a human story which demands thought, but also with a striking impression of the over-all effects of an atomic explosion—an excellent introduction to a necessary if somewhat melancholy study.

The same general material, but presented with a detailed emphasis on the essentially medical aspects, forms the basis of an informative article by J. J. Morton[1] published in 1957. Because of the importance of the subject and the relevance of Morton's article to this discussion, it is abstracted *in extenso* in this issue (see page 643). It is a useful study of a series of major atomic explosions and accidents, with particular reference to radiation burns. The effects of blast and heat in an atomic explosion are produced on a gigantic scale, but have little about them that is new from the medical standpoint. The management of resultant injuries follows the accepted principles of traumatic surgery. The special problems are those associated with ionizing radiation, and with these Morton has dealt more particularly. He points out that in the Hiroshima and Nagasaki explosions, people on the periphery of the 2000-metre zone, and some within the zone who were adequately shielded, escaped the ionizing radiation. It was otherwise with most of those within the 2000-metre zone and with those involved in the various other explosions studied—the bomb tests at Eniwetok, two nuclear accidents involving ten persons at the Los Alamos Scientific Laboratory, and the hydrogen bomb tests at Bikini, which affected not only the crew of the *Lucky Dragon* but also 28 American servicemen and over 200 Marshallese islanders. All suffered radiation effects in some degree. Apart from the Bikini explosion all the effects were due to direct radiation exposure at the time of the explosion, with this difference that at Hiroshima and Nagasaki there was total body irradiation from a distant source, whereas at Eniwetok and Los Alamos there was severe local irradiation damage, the radiation source being close at hand. In the Bikini explosion the exposure was different, coming from fall-out of powdered coral dust and radioactive fission products. Local burns caused by or complicated by radiation produced their own problems of healing, and generalized

[1] "Hiroshima", by John Hersey; 1958. Mitcham, Victoria: Penguin Books, Limited. 7" x 4", pp. 128. Price: 4s.

[2] "The Voyage of the Lucky Dragon", by Ralph E. Lapp; 1958. Mitcham, Victoria: Penguin Books, Limited. 7" x 4", pp. 176. Price: 4s.

[1] *Ann. Surg.*, 1957, 146:314 (September).

exposure to radiation produced the same broad picture, varying in severity and details of development with the extent of exposure. All this Morton has set out with notes on prophylaxis and treatment. More importantly his account indicates that protection from exposure to radiation is practicable in certain circumstances and that many of those exposed will recover, especially with adequate treatment. On the long-term genetic effects there would still seem to be much uncertainty. Perhaps some generations will have to pass before the effects in Hiroshima and Nagasaki are known, and we may hope fervently that no further mass human experiments of the same kind will take place in the meantime. At the same time we must be realistic about the possibilities of an atomic attack and consider the questions of medical organization involved. They are not easy to answer, but much thought has been given to them in Australia and overseas. They warrant separate discussion on another occasion.

Current Comment.

THE RESULTS OF TREATMENT OF OBESITY.

A VAST amount has been written on methods for the reduction of weight in obese persons, and two assumptions are commonly made: first, that weight-reduction programmes are effective; second, that they are harmless. Recent investigations have made it doubtful whether either of these assumptions is correct. The latest review on the subject has been given by A. Stunkard and M. McLaren-Hume.[1] They have reviewed the medical literature for the past 30 years and also the results of routine treatment of 100 consecutive obese persons in the Nutrition Clinic of the New York Hospital. The greater number of the published papers are of little value in assessing results of treatment because of several different types of omissions, particularly exclusion from reports of patients who did not remain in treatment or were otherwise "uncooperative". Such patients probably represent therapeutic failures. Of the very many papers examined, only eight remain in which the necessary information is completely given. A study of these papers reveals two significant points. The results of treatment for obesity—and different regimes were used in each of the papers—are remarkably similar and remarkably poor; for example, only one author reported even a 20 lb. weight loss in more than 29% of his patients. These reports were all written by persons with a particular interest in obesity, experts in the subject. In the eight papers 1378 patients were studied.

In order to obtain more precise data 100 persons admitted consecutively to the Nutrition Clinic of the New York Hospital were studied. Obesity was considered as a degree of body weight which exceeded by 20% the ideal weight of a person of medium build as established by the tables of the Metropolitan Life Insurance Company. Ninety-seven of the patients were women. The patients at the beginning were instructed in the use of balanced weight-reduction diets of 800 to 1500 Calories. They were seen at intervals of two to six weeks. Two and a half years later the patients' charts were reviewed to determine the outcome of the efforts at weight reduction. The lowest weight reached was considered the therapeutic effect. Only 12 of the 100 patients succeeded in losing more than 20 lbs. at any time during two years and only one lost more than 40 lbs. Furthermore 39 patients did not return to the Nutrition Clinic after their first visit. Maintenance of weight loss was difficult to appraise. Only six persons were able to maintain losses of 20 lbs. one year after treatment and two after two years. In four of the nine failures the patients regained all the weight they lost. Very similar results were noted in five published papers on weight reduction. Various authors have drawn attention to emotional disturbances in obese persons undergoing weight-reduction treatment. Of the 100 persons studied by Stunkard and McLaren-Hume 72 reported that they had attempted dieting previously. Of these 72 patients just over half reported the presence of symptoms during at least one reducing regime. The commonest complaints were "nervousness" and "weakness". Less frequent were "irritability", "fatigue" and "nausea".

Stunkard and McLaren-Hume attempted to find some possible indices of prognosis. Beyond the fact that men react more favourably to dietary treatment than do women, nothing came out of the investigation. They discussed the relation of weight-reducing procedures with members of the medical profession and with lay people. In recent years the ill effects ascribed to excess body weight in several diseases have received much attention, and weight reduction in the presence of obesity has been looked upon as a therapeutic imperative. Various lay organizations, particularly women's magazines, have taken this up vigorously, and now weight reduction has assumed the proportions of a national neurosis. When it became obvious that the human body obeys the second law of thermodynamics, it soon became a dictum that "all obesity comes from overeating". The physician's job was simply to explain that semi-starvation reduces fat stores and to prescribe a diet for this purpose. If the patient lost weight as predicted, everything was right; if not, the patient was dismissed as uncooperative or gluttonous. That failure might itself be a medical problem was seldom considered. If the patient eats too much why does she do so? This is the big problem, and at present there is no answer, but obviously reduced diets do not always, or indeed often, affect the cause, whatever it is. It is clear from the results reported in this paper and in several others which have appeared lately that a new approach to the study of obesity is necessary.

[1] *A.M.A. Arch. Int. Med.*, 1959, 103: 79 (January).

STONE-FISH AND OTHER ANTIVENENES.

AN ARTICLE describing the successful preparation of an antivenene against the venom of the stone fish (*Synanceja trachynis*) by Dr. S. Wiener, which appears on page 620 of this issue, is yet another success for the immunologists, who to many of us now appear to be able to produce antisera to any noxious substance with the regularity and facility of a conjurer pulling rabbits out of a hat. However, in a personal communication Dr. Wiener tells us that the problem is not always straightforward. Some venoms are complex substances of heavy molecular weight which readily excite the production of antibodies, and the venoms of the stone fish and the red-back spider come into this category. Other venoms which are more stable substances of relatively low molecular weight have poor antigenic properties, and it is not possible to produce an antivenene against these by conventional methods. Unfortunately, the venom of the funnel-web spider comes under this heading; but Dr. Wiener hopes that if such non-antigenic venoms can be purified in sufficient quantity and coupled to a protein, they may become antigenic.

The occasion for the use of such antivenenes arises relatively rarely, but perhaps more commonly than one might suppose. We are informed by Dr. Wiener that in the past two years the Commonwealth Serum Laboratories have received some sixty reports of the effective use of red-back spider antivenene. On analogy one may therefore expect that, now that stone-fish antivenene is available, reports of its effect in cases of stone-fish sting will soon be available. There are centres in North Queensland where at least two or three patients with stone-fish stings may be seen each year, and it would be particularly helpful if someone interested

was to make a trial comparing the effects of antivenene with those of the local injection of emetine hydrochloride, for which dramatic claims have been made.[1] Whichever is preferred, it is certainly satisfactory to have two lines of treatment available for this exceedingly painful and occasionally dangerous injury. Meantime it should be noted that the Commonwealth Serum Laboratories have a quantity of the stone-fish antivenene available for clinical trial.

PULMONARY ALVEOLAR MICROLITHIASIS.

PULMONARY ALVEOLAR MICROLITHIASIS is a rare condition which, according to J. Gough,[2] was first described in Germany by Leicher in 1949. When Gough wrote his paper the condition was still little known, and he tells a story of a radiograph, published in a textbook of X-ray diagnosis as an example of gross chronic hæmosiderosis; subsequently, after the publication of the picture, the patient concerned died, and autopsy revealed that the radio-opacity was due, not to hæmosiderosis, but to microlithiasis. In a recent paper, W. R. Cole[3] discusses the clinical picture, the pathological findings and the radiological features of the condition. He states that it is characterized by the formation of tiny calculi or calcospherites in the alveoli extensively throughout the lungs. The condition remains symptomless for many years, and several cases have been discovered by routine chest surveys in which no lesion was suspected. In these cases the striking radiological appearances are quite out of proportion to the respiratory symptoms, which may be completely absent or negligible. Only in the later stages of the disease is there evidence of pulmonary insufficiency, when increasing dyspnœa occurs. There may be emphysema, cough and increased sputum, and clubbing of the fingers is occasionally seen. The condition is slowly progressive, and the patient may ultimately die of right-sided heart failure or of actual loss of breathing capacity due to filling of the alveoli by the calculi. The results of laboratory tests are at first entirely negative, but later there may be evidence of reduced pulmonary ventilation, compensatory polycythæmia or electrocardiographic changes due to right ventricular hypertrophy. The condition is not associated with any change of serum calcium, phosphorus or phosphatase values, and in no case has any disorder of the parathyroid glands been described.

At autopsy, the gross specimen of the lung is described as feeling like sandpaper; it is gritty to cut and studded with tiny calculi. In more advanced cases emphysematous blebs may be found at the apices. The lungs are heavy and will sink in water. Microscopically the tiny calculi can be seen lying within the alveoli, a great number of which are involved. The calculi lie freely within the lumen of each alveolus, and in most areas the alveolar walls show no pathological change. In some areas there may be a monocytic cellular infiltration or fibrous tissue reaction in the interstitial tissue of the lung. Occasional giant cells have been described in some cases and also actual bone formation. In spite of the great number of calculi, they are rarely noted in the sputum, presumably because they lie beyond the reach of the normal bronchial drainage mechanism.

Cole states that the radiological picture is the most outstanding feature of the disorder. A generalized fine but dense miliary mottling is seen throughout the lungs, heavy at the bases and around the hilar areas; in the latter regions the shadows coalesce to form larger opacities. On examination with a magnifying glass the individual nature of each opacity is seen, especially toward the lung periphery. Often a thin white line can be seen over the subpleural surfaces of the lungs, or in the interlobar fissures, or mediastinal outlines, simulating a layer of calcium, but at fluoroscopy no hindrance to the normal movement of the intrathoracic structures is seen. The degree of opacity of the lungs varies in different cases according to the extent of alveolar involvement and tends to be greater in the thicker part of the lung, the larger nodules being due to overlap of the concretions or to the formation of small bony islands. In many cases the normal mediastinal and hilar outlines are obscured by the density of the pulmonary shadows unless the film exposure is considerably increased, when the lungs appear more opaque than the adjacent soft tissues. The condition is found to be slowly progressive, the lungs becoming denser, and emphysematous blebs may devolop, but there is a great deal of individual variation both in the rate of progress and in the extent of alveolar involvement. According to Cole, of the many types of fine and diffuse miliary mottling, the number which show any real similarity to this condition are very few. Most types of true miliary mottling are made up of opacities of soft tissue density, and miliary tuberculosis must head this list in order of importance. In none of the inflammatory diseases is the individual lesion a sharply defined one having the density of calcium. Some diseases, such as histoplasmosis, may, in a chronic or healed state, produce multiple calcified nodules, but these are scattered and relatively large foci, quite unlike the widespread alveolar calculi. Sarcoidosis is radiologically similar in its picture of widespread pulmonary involvement, but again the individual lesions are not calcified, and there is often associated mediastinal adenopathy. As already mentioned, hæmosiderosis has been confused with this disease, but again the opacities are soft, not of calcium density, and in the adult there will probably be evidence of mitral stenosis and pulmonary venous congestion. (In the case quoted earlier, the patient suffered from mitral stenosis as well.) A history of occupational exposure is an essential factor in the pneumonokonioses, and the miliary shadowing is a soft one in nearly all types. However, Coles admits that confusion may be caused by tin oxide or barium powder, which can produce a dense mottling in the lung-fields, and also by the presence of "Lipiodol" in the lungs. Like all rare entities, once the existence of pulmonary microlithiasis became generally known, other cases came to light, but it still appears to be a very uncommon condition.

[1] MED. J. AUST., 1958, 2:218.
[2] *Lancet*, 1955, 1:161 (January 22).
[3] *J. Fac. Radiol. (Lond.)*, 1959, 10:54, January.

SKIN CANCER SURVEY.

IT is well known that in the northern parts of Australia the incidence of cancers of the skin, both epithelioma and rodent ulcer, is one of the highest in the world, and it is generally recognized that this is because we have a relatively fair-skinned population much addicted to exposing themselves freely to the sun. Generally speaking, in other parts of the world of corresponding latitudes most of the population, especially that part of it accustomed to working out-of-doors, consists of individuals with more pigmented skins, who have little susceptibility to skin cancers. One consequence of this state of affairs is that it provides Australian investigators with unique opportunities for study into the causation, prevention and treatment of skin cancer. It is therefore interesting to note the activities of the Skin Cancer Research Project of the University of Queensland. With the cooperation of the Queensland Cane Growers' Council a pilot survey of the incidence of skin cancer has been conducted in the Ayr district. The results of this survey have encouraged its organizers to extend the survey to include the entire coastal strip of Queensland by forwarding *questionnaires* to cane farmers in the Cairns, Mackay, Bundaberg, Nambour and Beenleigh areas. To compare coastal areas with western areas *questionnaires* are also being sent to graziers in inland districts. This survey is presumably intended as a foundation for more exact investigations into other aspects of skin cancer.

The time has certainly come to go beyond merely superficial surveys of incidence to more fundamental investigations, if the financial and other resources are available.

Abstracts from Medical Literature.

PATHOLOGY.

Calcium and Phosphorus Metabolism after Surgery.

K. W. STARR, K. N. WYNNE AND S. H. CHARLTON (*Nature*, November 29, 1958) report the results of an investigation into calcium and phosphorus metabolism in patients undergoing major surgery. They note that the view is widely held that major surgical procedures may encourage the growth of metastases in patients with certain types of cancer. The investigation was undertaken in view of the possibility that operative stress may favour the spread of tumours by affecting adhesion between cells, and of the known relationship between lack of adhesiveness and low calcium content. Urinary excretion studies were carried out on 23 patients, the urine being collected every four hours. A characteristic calcium and phosphorus excretion pattern was found in which, after uncomplicated major surgery, there was a phosphorus diuresis which was usually associated with retention of calcium. The authors suggest that these observations are consistent with a post-operative calcium mobilization which, in most cases, could be associated with an increase in parathyroid activity. They state that the possibility that surgical trauma produces a condition in which there is a local or systemic demand for calcium by the tissues is being investigated, as well as the possibility that changes in the concentration of calcium in the tissues may favour the spread and establishment of metastases.

Pulmonary Fat Embolism.

J. L. HICKEY AND V. A. STEMBRIDGE (*J. Aviat. Med.*, November, 1958) have found that amongst 230 fatalities in aircraft accidents, fat embolism was found in the lung on 120 occasions. Bone marrow embolism was noted in 17 cases, cerebral tissue embolism in three, and liver tissue in two. Fat embolism of marked degree was most common in subjects whose survival could not have been more than momentary. In 50 routine hospital autopsies fat embolism was found in one instance only, and that was in a man who died after laryngectomy for carcinoma. In another 50 autopsies performed in medico-legal cases in which there was a history of trauma, violence and unexplained death, there were 11 examples of fat embolism and one of bone marrow embolism. The occurrence and mechanism of fat embolism in fatal decompression sickness is discussed and a case is presented. The authors suggest that nitrogen gas bubbles liberated in fat cells rupture them, and that the liberated fat then enters the venous blood-stream.

Carcinoma-in-situ of the Cervix.

R. E. L. NESBITT, JUNIOR, AND A. A. STEIN (*Surg. Gynec. Obstet.*, August, 1958) discuss the histochemical evaluation of carcinoma-in-situ of the cervix uteri. They subjected cervical tissues from 42 proved cases of carcinoma-in-situ to careful histological and cytochemical study, in an attempt to find specific histological criteria for diagnosis and a reliable method for identification of the basement membrane, and to evaluate the biological characteristics of the lesion. Specimens were stained with hæmatoxylin and eosin and by the periodic-acid-Schiff technique. The latter was found useful in identifying the basement membrane. They state that carcinoma-in-situ of the ectocervix is a distinct entity characterized by a typical basal-cell hyperplasia with a failure of cell maturation. In the endocervix this lesion results from reserve-cell hyperplasia with absolute failure in differentiation as well as in maturation. The authors discuss the differentiation of carcinoma-in-situ from other types of cell disorder, and emphasize the importance of establishing precise and uniform histological criteria for the diagnosis of carcinoma-in-situ. They state that they have attempted to describe the cellular changes and biological characteristics of carcinoma-in-situ, as well as other exocervical and endocervical lesions, with a view to standardizing diagnostic criteria.

Isotopic Evaluation of Thyroid Nodules.

H. P. GROESBECK (*Cancer*, January-February, 1959) has written two papers which deal respectively with the pre-operative diagnosis of thyroid carcinoma and the post-operative management. "Thyrograms" were taken of 527 patients after the administration of I^{131}, and in 253 who were treated surgically the isotopic function was correlated with the histological findings. There were 39 patients with cancer in this group. The author finds that in the presence of functioning thyroid tissue, carcinoma rarely if ever exhibits normal function, and that a nodule with decreased or absent function therefore has a much greater likelihood of being malignant. Twenty patients were studied with I^{131} after surgery for carcinoma of the thyroid. Of 15 patients who had purportedly undergone total thyroidectomy, nine had residual functioning tissue in the thyroid area and six showed complete absence of functioning thyroid tissue. Routine "thyrograms" were found to afford accurate information concerning the presence and location of functioning metastases. Isotopic studies were found to be a very useful adjunct to the clinical evaluation of the patient before operation, and after operation it enabled the surgeon to determine whether thyroidectomy had really been complete.

Scleroderma with Lung Changes.

D. H. COLLINS, C. S. DARKE AND O. G. DODGE (*J. Path. Bact.*, October, 1958) have described the case of a woman, aged 45 years, who had suffered from scleroderma for many years and died from bronchiolar (alveolar-cell) carcinoma. The tumour had spread widely through the right lung, and metastases were present in the hilar and mediastinal lymph glands and in the left adrenal. Much of the skin of face and limbs was sclerodermatous, and other lesions characteristic of the disease were found in the heart and lungs. Extensive venous thrombosis and pulmonary infarction were terminal events. Fibrosis and honeycomb cysts were present in both lungs, and in the right lung there were varying degrees of epithelial proliferation. Four cases have previously been reported of bronchiolar (alveolar-cell) carcinoma arising in a sclerodermatous lung. The authors believe the chain of events to be: scleroderma, pulmonary fibrosis, honeycomb lung, adenomatosis, carcinoma.

Encephalopathy after Minor Head Injury.

J. DENST, D. W. SINTON AND K. T. NEUBUERGER (*A.M.A. Arch. Path.*, February, 1959) have described the case of an adolescent Negro who developed chronic encephalopathy with dementia following a single minor head injury incurred in a wrestling match. It was characterized by severe demyelination throughout the white matter of the cerebral hemispheres. An incidental subdural hæmorrhage and small softenings of the basal ganglia were present. The demyelination is thought to have supervened upon post-traumatic œdema. The cortical atrophy was attributed to thixotropy.

Cytodetection of Preclinical Carcinoma of Cervix.

E. H. SOULE AND D. C. DAHLIN (*Proc. Mayo Clin.*, January 7, 1959) have reviewed their experiences in the cytodetection of carcinoma of the cervix. In the ten-year period 1948 to 1957, a total of 678 examples of preclinical carcinoma were discovered by examination of 90,257 smears. Fifty-five (8%) of these lesions proved to be infiltrating carcinomata. There were 673 examples of squamous cell carcinoma of the cervix, three of adenocarcinoma of the cervix, and two of endometrial adenocarcinoma. During the same period examination of 14,440 repeat smears resulted in the detection of 27 preclinical neoplasms. Of all women shedding atypical cells, 70% of those examined by biopsy were found to have a carcinoma, while 68% of those without carcinoma had epithelial abnormalities to account for the atypical cells.

Superior Vena Caval Obstruction.

H. J. FAILOR, J. E. EDWARDS AND C. H. HODGSON (*Proc. Mayo Clin.*, December 10, 1958) have reviewed the pathological findings in 33 examples of superior vena caval obstruction. The most frequent cause was carcinoma of the lung, comprising 18 cases. In each case there was invasion and penetration of the superior vena cava, and in 11 the azygos vein was also invaded. Malignant tumours other than carcinoma of the lung were responsible in 10 cases (five lymphomata, three primary malignant tumours and two metastatic carcinomata). Benign lesions caused obstruction of the superior vena cava in five cases. In four this was due to chronic mediastinitis and in one to a teratoma.

Fatal Chlorpromazine Jaundice.

A. E. RODIN AND D. M. ROBINSON (*A.M.A. Arch. Path.*, August, 1958) present the case of a woman aged 43 years who was receiving chlorpromazine for a depressive state associated with agitation.

She received, in all, 1800 mg. of the drug over a period of nine days. Thirteen days after cessation of the treatment she developed jaundice and three weeks later she was submitted to laparotomy because of increasing obstructive jaundice. The jaundice became more severe after operation, and her mental state deteriorated. She died in a shocked state 40 days after the onset of jaundice. In addition to the usual infiltrates in the portal tracts and the centrilobular bile stasis found in chlorpromazine jaundice, there was some centrilobular hepatocellular degeneration. Death is ascribed to the action of chlorpromazine.

THERAPEUTICS.

Trial of a New Cytostatic Agent.

A. RAVINA, T. GROSZ AND M. PESTEL (*Presse méd.*, February 28, 1959) report on the results obtained with DG 428, a new cytostatic synthesized by K. Westphall. The substance is an antimetabolite of thymine, and is chemically related to it. The authors have used DG 428 in the treatment of a variety of tumours, but it proved effective only in cases of cancer (especially papilloma) of the bladder; several of these patients were markedly improved, though none could be considered cured. The authors observed that certain cytostatics have also an antiinfectious action; this is particularly apparent in DG 428. They suggest that, as Domagk recommended, greater trial should be made of the resources of chemotherapy in preventing the transformation of benign into malignant tumours. Their results, and the slight toxicity of the drug, indicate that it would be worth while giving longer courses of treatment and larger doses than they used. It may be valuable as pre-operative and post-operative treatment of tumours of the bladder.

Cortisone and ACTH in Mumps Meningo-Encephalitis.

J. K. SPITZNAGEL (*Ann. intern. Med.*, July, 1958) reports on the results of treatment of five patients with severe or moderately severe mumps meningo-encephalitis. Diagnosis was confirmed by lumbar puncture in all cases, and complement fixation titres were determined in four of the cases. Four patients received cortisone, administered in doses of 200 to 300 mg. per day, and one patient ACTH in doses of 60 mg. per day. In all cases but one, the drugs were discontinued by progressive decrements. Cortisone and ACTH appeared to produce rapid remission of headache, nausea, anorexia, vomiting, photophobia, lethargy, delirium and neck rigidity. Fever, although it subsided rapidly, tended to recur for short periods of time, accompanied by minor recurrence of other symptoms. Orchitis developed in one patient during cortisone therapy. This patient, and one other, suffered additional salivary gland involvement during therapy. Abrupt termination of therapy n one case after three doses of cortisone resulted in a dramatic recurrence of previous symptoms. The duration of mumps in these patients was not shown to differ from that in patients not receiving cortisone or ACTH, and no evidence of residual disease of the nervous system was detected in any of the patients.

Systemic Lupus Erythematosus.

E. L. DUBOIS (*J. Amer. med. Ass.*, July 26, 1958) describes the treatment of systemic lupus erythematosus with triamcinoline. He states that the initial dose of triamcinoline varies between 4 mg. and 40 mg. daily according to the severity of the condition, and that the maintenance dose is 8 mg. to 96 mg. per day. The clinical picture, the hæmoglobin level and the degree of renal involvement (if present) are guides to therapy. Hæmoglobin levels near the normal are an indication for gradual lowering of the dose by decrements of 10%. Mild relapses lasting a few days do not necessitate an increase of the dose. The author reports the results in 29 patients so treated, 22 females and seven males. The average age at the onset of illness was 26 years. The average duration of treatment with triamcinoline was 4·3 months. Patients reacted variously to treatment, which had to be watched carefully. Triamcinoline was found to be slightly more effective than prednisone, hydrocortisone and prednisolone. Triamcinoline acetate was as effective as the alcohol derivative. Normal salt intake was given to all except four patients who had œdema due to renal involvement. An ulcer diet with anticholinergic drugs was given to patients with a history of duodenal ulcer or with epigastric distress. Cutaneous side effects, especially moon-face, hirsutism and striæ, were more marked than with older steroids, and muscle weakness was very marked in six patients. Eighteen patients lost weight. Generally, the clinical picture improved. Fever abated in 24 hours, joint pains, pleural effusion and cutaneous lesions subsided in one or two weeks. Retinal changes, anæmia, adenopathy and cachexia improved over several weeks. Mild renal abnormalities responded, but long-standing renal changes, especially with hypertension, were unaffected by hormone therapy. Weakness of the legs was very marked in some patients, and in six cases cessation of steroid therapy was necessary. No male developed this syndrome.

Bacteriostatic Action of Chlorpromazine.

M. POPPER AND V. LORIAN (*Presse méd.*, January 31, 1959) have studied the bacteriostatic properties of chlorpromazine. They state that it has a bacteriostatic action on staphylococci and *Bacillus mesentericus* in concentrations ranging from 15γ to 60γ per cubic centimetre. It also has a bacteriostatic action on the tubercle bacillus, but only in concentrations above 250γ per cubic centimetre. In a concentration of 10γ per cubic centimetre, it has a potentiating action on antibiotics varying between 25% and 50%. The practical corollary of these findings is that chlorpromazine, which when given by intramuscular injection can reach a concentration of 0·5γ to 5γ per cubic centimetre in the blood, may eventually produce bacteriostasis and potentiate the action of antibiotics given; it certainly never stimulates the multiplication of microorganisms and never diminishes the effect of antibiotics. Consequently, when a course of chlorpromazine treatment is given, it is never necessary to increase the dosage of antibiotics or to take other precautions, such as those required during treatment with cortisone.

Weight Reduction.

R. J. GODEK *et alii* (*J. Amer. med. Ass.*, May 24, 1958) record a study of a new drug for reducing weight, "Levonor" or 1-phenyl-2-aminopropane alginate. Eighty overweight patients were treated, 5 mg. tablets being given thrice daily half an hour before meals. A diet was also prescribed to help reduce the weight. An average weight loss of 2 lb. per week was recorded. This drug was better tolerated than most appetite suppressors. It had no stimulating effect on the nervous system and did not cause insomnia or other side effects. It could be given in the early evening without preventing sleep, and thus was useful in suppressing appetite and avoiding the taking of night snacks, to which some patients are prone. This drug did not help depressed patients or produce psychic stimulation.

Ristocetin.

G. L. CALVY AND R. SCHUMACHER (*J. Amer. med. Ass.*, July 26, 1958) report the use of ristocetin ("Spontin") in treatment of infections due to Gram-positive organisms. They state that ristocetin was isolated from the beer of a new species of Actinomycetaceæ, *Nocardia livida*. It was used to treat resistant staphylococcal pneumonia in 17 patients with good results. The dosage was 25 mg. per kilogram of body weight per day, given in divided doses, that is, between one and two grammes daily. The required amount was dissolved in 30 to 100 ml. of 5% glucose solution, and given slowly over 10 to 30 minutes. The solution was injected into the tubing of an intravenous infusion system, and 100 to 200 ml. of glucose solution was run in at the termination of each injection of the drug. Larger doses may cause leucopenia. The drug is excreted mainly through the kidneys, and children, old people and those with renal impairment should receive smaller doses.

Benzoquinone-guanylhydrazone-thiosemicarbazone.

A. RAVINA (*Presse méd.*, January 17, 1959) reports the use of benzoquinone-guanylhydrazone-thiosemicarbazone in the treatment of infections of the mouth and pharynx. He states that the drug has a striking curative action, particularly in streptococcal and pneumococcal tonsillitis and throat infections and is well tolerated. Its effects are as good as those of the sulphonamides and antibiotics, and it is free from the danger of provoking allergic reactions or causing alteration in the intestinal flora. It can be given to ambulatory patients, and has been shown to have a prophylactic action when there is a risk of contagion, and after tonsillectomy or dental extractions. It is a valuable agent in the treatment of stomatitis and sore throat of various types. The author states that, as far as he knows, it is the first thiosemicarbazone derivative to have a bacteriostatic and bactericidal effect on the common pathogens.

Special Article.

TRITIUM, A SERVANT OF MEDICINE.[1]

TRITIUM is a portentous word. It was introduced to the awareness of the world as a component of the hydrogen bomb. For peaceful purposes it is the element which, in combination with deuterium, will release 17,000,000 electron volts of energy in a successful fusion process. For such purposes tritium is man-made, but through all the æons of time Nature (although we did not know it until recently) has been manufacturing it by the bombardment of the elements of our upper atmosphere by cosmic rays from outer space. Tritium is radioactive hydrogen.

One of the interesting disclosures at the Second International Conference on the Peaceful Uses of Atomic Energy in Geneva last summer was the fact that this radioisotope, capable of releasing such pent-up power, is one of the mildest, most docile and most inquisitive servants of biology and medicine. It has a half-life of twelve and a half years, and it releases soft beta rays. Being hydrogen, it combines with oxygen to form water and can be absorbed, as water is, in the tissues and the cells of the body. Once it is so lodged and the cellular tissue is sectioned and placed on a photographic plate, the tritium will reveal itself as a clearly defined image—will photograph itself.

A great many papers on tritium were submitted at the conference, showing the wide possibilities of this new "tool" which has become available in adequate amounts and at fairly reasonable cost. One example was the study, with tritium, of the routes travelled by insulin in the body. The insulin was recrystallized, to include the radioactive tritium, and was found to retain its full biological potency. When injected into the veins of rats it could be traced to the liver, to the pituitary gland and to the adrenal glands. This route marking was extremely interesting since all three glands are involved in the regulation of carbohydrate metabolism.

Secrets of Life.

Even more fundamental is the access which tritium has given to the body cells. By incorporating it into thymidine, a precursor of desoxyribonucleic acid (DNA), it is possible to study the synthesis of this acid, which holds the secret of life, because it is a chemical which reproduces itself. It is possible, when DNA has been labelled in this way, to study chromosome duplication within a single cell. It has been used in animals and man to study the mechanism of cell production, because it is incorporated only in cells which are actively multiplying.

Thus tritium, harmless in any concentrations ever likely to be used in research or in medicine, will probably be as useful as C^{14}, radioactive carbon, in the study of the metabolic processes. Carbon is the basis of all organic chemistry. Its radioactive form, produced in nuclear reactors, has a half-life of 5000 years—long enough for the research worker to complete his experiments! It can be used to show, in the living processes, how sugars, starches, fats and proteins are built up and how they are re-employed in the body. For example, glucose compounded with C^{14} will first mix with the glucose of the blood, and then it must enter the cells. It is possible to show how it penetrates the cell membrane and how the glucose is broken up and its elements are dispensed to create new chemicals to feed, to build or to replace the tissues.

At any one of the stages it can be detected by the ingenious but essentially simple device of chromatography; so that it is possible, with detectors, to determine all the intermediate stages of what has hitherto been an invisible process.

Photosynthesis.

In the same way, as revealed at the conference, C^{14} can explain an already successful fusion device in the service of man. For the sun is a fusion reactor, and the energy which it releases is picked up by plants and converted into the foods we eat by the process of photosynthesis. This process may, in the long run, be more important than the release of fusion energy for industry because it will, fundamentally, increase our knowledge of the foods on which our multiplying population depends for its survival. In the extreme, it could mean that we would make our foods from the elements without dependence on soil or even on the plants.

At the first "Peaceful Uses" conference, the scientists were able to show what was virtually the flow sheet, or ground plan, of the "chemical factory" by which the plant converts the energy of the sun into sugars and starches. The technique is to grow the plants in an atmosphere which contains radioactive carbon dioxide; the radioactive carbon, like a night watchman clocking in at his check points, will record each stage. At the second conference we heard of the extension of this by adding O^{15} and radioactive hydrogen (tritium). O^{15} is not itself radioactive, but it can be made so by being bombarded with protons when it becomes F^{15}, which is radioactive and easy to identify and to measure. Thus the three major elements of photosynthesis are now available.

Beyond the photosynthetic carbon cycle is the Krebs cycle, which leads on to the processes which produce fat and protein. This too can be followed by radioisotopes.

Labelling Cells.

Every natural element has its useful man-made isotopes. At Geneva we heard accounts of how radioactive phosphorus had been used to "label" red blood cells and to establish the life-span of human cells at between 110 and 130 days. This has had an immediate value in blood transfusion, because after blood has been stored for some time the cells may appear normal under the microscope and yet be rapidly destroyed when they are transferred into a patient. Evidence was produced that whole blood can be safely stored in acid-citrate-dextrose solution for periods up to 21 days and that survival can be prolonged by the addition of inosine or adenosine.

There were disquieting disclosures about radioactive elements in the skeleton—"disquieting" because of radiostrontium. This element did not exist in Nature, but is produced in nuclear reactors and by the explosion of the H-bombs. It is a "cousin" of calcium and, if it gets into the body, will, like calcium, go into the formation of bone, particularly in children whose bones are growing. It has been shown by researches that the radiostrontium lodges not only deep in the bone itself but in the heart of the bone-crystals, where it cannot be reached by any chemical which might otherwise have removed it.

Apart from this sombre warning, the work on bones has revealed much that was hitherto unknown. For instance, it has shown that bone is a very dynamic structure, not inactive tissue. One paper presented at the conference described the distribution of radiocalcium in the tissues and skeleton of a mouse. The injected animals were killed at intervals of from ten seconds to ten minutes by deep-freezing them in liquid hydrogen. This instantly arrested the process, and the sections placed on a photographic plate produced images which were, in effect, a slow-motion picture of the progress of the calcium. At ten seconds the calcium was chiefly in the blood, but by forty seconds it was beginning to concentrate in the bone.

The shades of Vesalius, Harvey, Claude Bernard and Pavlov, if they had joined the 6000 participants at this conference, would have heard how their researches had become radioactive. Here, for Vesalius, was the account of how the "fabric" of the body was being charted not *post mortem* but as a living process. Harvey would have heard how by breathing radioactive gases, the scientists had obtained new information about the left side of the heart, the circulatory system and the lungs. Bernard would have discovered how the work which he initiated on the endocrine glands was becoming audible and visible with the use of Geiger counters, scintillometers and radioautographs. Pavlov would have heard his compatriots describing how to locate tumours in the brain and study reflexes in the nervous system.

The living liver has been mapped by radioactive forms of gold, iodine and labelled rose-bengal and has appeared as a scintillating picture.

Studies of the use of radioisotopes in the brains of animals and man have suggested possible techniques for the treatment of Parkinson's disease. Methods for locating brain tumours and lesions which have hitherto not been very successful are being improved by the search for elements which (like boron, the first to be tried) will concentrate in the diseased brain tissue and, when irradiated by an outside source, will release atomic particles. Detectors will pick up these rays and, like direction finders, will fix the bearing of the lesion.

Hundreds of papers on the medical and biological uses of radioisotopes were submitted to the conference from

[1] The second of three articles (slightly modified) written for WHO by Ritchie Calder, a well known British science writer, on health aspects of atomic energy as discussed at a United Nations Conference on the Peaceful Uses of Atomic Energy, held in Geneva in 1958.

all over the world. Apart from the use of radioiodine, which concentrates in the thyroid gland and by internal radiation can treat diseased tissue, "isotopes-by-absorption" have not yet proved a very effective treatment. The idea of using chemicals with affinities to specific parts of the body as a means of internal treatment is an attractive one, but much more knowledge is needed to give precision. On the other hand, the direct injection of isotopes into the body tissues and cavities has proved useful in diagnosis and in treatment. The most effective procedure of treatment by radioisotopes, however, is still teletherapy—the use of radioactive cobalt and radiocæsium as external sources of beams, as in the case of X rays and radium.

Conclusion.

"Each new diagnostic procedure of radioisotopes," said Professor R. H. Chamberlain of the University of Pennsylvania in a key-note speech to the conference, "adds dimensions to our knowledge of the intricacies of the human body. Practically all the organs and parts of the body are now accessible to study."

However, he warned his colleagues against the "glamour" of radioisotopes and atomic energy, pointing out that doctors must not be dazzled by novelty. They could be misled by inexperience into dangers for their patients or diverted from conventional methods which were often better.

RITCHIE CALDER.

Special Abstract.

RADIATION BURNS DUE TO ATOMIC EXPLOSIONS.

THE following extended abstract is referred to in a leading article in this issue.

J. J. MORTON (*Ann. Surg.*, September, 1957) discusses radiation burns due to atomic explosions. He states that at the atomic explosions of Hiroshima and Nagasaki injuries were due to a combination of intense mechanical energy (blast), instantaneous heat (flash) and ionizing radiation. People within the 2000-metre zone were exposed to all three and, in addition, to trauma from flying objects and to ordinary flame burns from the fires caused. People on the periphery of this zone, and some who were adequately shielded in the zone, escaped the ionizing radiation. Burns complicated by ionizing radiation healed more slowly than those not so complicated. As the atomic bombs were exploded in the air well above these Japanese cities, the ionizing radiation travelled a considerable distance through moist air before making contact with the individuals exposed to their action. Thus the radiation doses in the fully exposed Japanese were uniformly distributed throughout their bodies. These radiation effects were delivered in a very short period of time—98% of the gamma rays and neutrons by the end of one minute.

Morton also studied patients suffering burns from radioactive materials after one of the bomb tests at Eniwetok. These men received severe radiation burns of the hands with a lesser amount of total body irradiation. It was estimated that the total body irradiation did not exceed 15*r* of gamma rays in any individual, but their hands were subjected to from 3000 to 16,000 röntgen equivalent physical (rep) doses of radiation to the outer surface of the skin. These beta rays were 99% absorbed in the outer 6 mm. of tissue, and the dosages below this depth were from 300 to 1600 rep. This type of radiation burn was essentially a localized beta burn which was very severe for a limited amount of tissue. Two nuclear accidents, which occurred at the Los Alamos Scientific Laboratory, exposed 10 persons to bursts of penetrating ionizing radiation causing the death of two of them. The others received varying doses of radiations, so that differing types of reaction were noted. One survivor showed the typical acute radiation syndrome, whereas four others manifested blood damage. The radiations in these patients were chiefly fast neutrons and hard gamma rays. The neutrons were absorbed in the few inches of tissue near the reactors. In the fatally injured persons a very heavy dose of radiation was received in the hands and over the abdomen. These examples of radiation burns received in the field and in the laboratories differed from the atomic bomb injuries produced in the bombed Japanese cities. In the latter the radiation effects were total body irradiation from a distant source, whereas in the former there was severe local irradiation damage, the radiation source being close at hand.

In the hydrogen bomb test at Bikini in 1954 another type of radiation burn was experienced due to the fall-out of powdered coral dust which came down through the explosion cloud bringing radioactive fission products of the rare earths with it. This dust was carried widely by unexpected air currents. The fall-out of this radioactive dust exposed Americans, Japanese and Marshallese to burns of the uncovered surfaces of the body. Morton was fortunate in that he later saw the Japanese who had been on a fishing vessel (*Fukuryu Maru*) 70 miles away from the bomb explosion. The Japanese sailors saw the flash of the explosion, and three hours later a fall of powdery material like snow covered their vessel. They remained another five hours in the area. When they arrived at their home port of Yaizu, they were examined by Japanese physicians. The sailors had washed off the dust with a detergent as well as they could at the time it fell. But for two weeks they had lived on a radioactive ship, breathing contaminated air and eating some of the fish which was probably radioactive. Much white dust remained in the cracks of the deck, on the pilot house and in the life boats and in recesses about the ship. Coils of rope and all sorts of gear usually found on such fishing craft trapped radioactive dust. Two sailors were examined some 19 days after their exposure to the fall-out. They had no complaints, but both had identical lesions. The exposed areas of the face, neck and skin of the forearms showed intense deep brownish pigmentation and roughness with desquamation. Blistering was apparent on the hands. There were eroded areas on their left ears and several pigmented spots on the abdomen. The hair was dry and came out easily. Acute conjunctivitis was present. The eroded surfaces on the ears gradually spread during the next week, epilation continued, and scabbing appeared in areas of the scalp. There was also mild anæmia with decrease of platelets and of parenchymal cells in the bone marrow. Morton states that about half of the sailors on the fishing vessel had noticed a burning itching sensation shortly after the fall-out. Two had loss of appetite, with diarrhœa at times. Three of the patients complained of general malaise and three of a headache. Otherwise there was no evidence of general intoxication. The appearance of the burns in these patients appeared to be that following exposure to beta rays. Examination of 24-hour specimens of urine showed the presence of strontium 89, barium and the rare earths, but not the dreaded strontium 90.

Morton was then able to study the Americans and many Marshallese who were victims of the same fall-out but received treatment soon after their exposure. Two hundred and sixty-seven individuals had been exposed to estimated total gamma radiations in the air from 14*r* to 175*r*. The American servicemen, 28 in number, were about 150 miles east of Bikini, and there was a fall-out of a mist-like dust some seven hours after the explosion; it was estimated that they received some 78*r* of gamma radiation in air. The Americans had realized the danger from this dust and had remained inside aluminium buildings, bathed and put on extra clothing. None developed ulcerating lesions or had gastro-intestinal symptoms. They noted itching and burning of the skin during the first 24 hours in one or two instances. No erythema developed, and superficial skin reactions appeared only in the third week after exposure. Less than half the Americans developed very mild beta skin lesions, which apparently healed normally.

The Marshallese were on the atolls of Rongelap, Ailinginae and Utirik at the time of the bomb test. Ailinginae is only about 80 miles east of Bikini, but it is a little south and was on the edge of the fall-out. There were 18 Marshallese there when the mist-like dust arrived some six hours after the explosion, and it is estimated that they received 69*r* of gamma radiation in air. On Utirik some 310 miles east of Bikini were 157 Marshallese. A fall-out did not occur until 22 hours after the explosion, and it is estimated that the patients received 14*r* of gamma radiation in air. The 64 Marshallese on Rongelap, 120 miles from the explosion, saw a heavy snow-like fall-out from four to six hours after the explosion, corresponding with the type of fall-out on the Japanese fishing vessels. These Marshallese received some 175*r* of gamma radiation in air. Itching and burning of the skin occurred in 28% of the Rongelap group, in 20% of the Ailinginae group, in 5% of the Americans and in none of the Utirik people. None of the Marshallese on Utirik had gastro-intestinal symptoms. Only one of the Marshallese on Ailinginae was nauseated. But two-thirds of the Rongelap Marshallese were nauseated during the first two days, and one-tenth vomited and had diarrhœa. The Rongelap people were the first to develop skin lesions and epilation, commencing some 12 to 14 days after the explosion, whereas the Ailinginae and the Americans developed skin lesions one week later than this. The lesions were spotty and occurred on exposed portions of the body; most were superficial pigmented macules, papules or raised plaques, small at first but tending to coalesce. An initial rise in the total leucocyte count in the first two

days, due to neutrophil increase, was followed by a lowering of the count persisting over the next five to six weeks. Early relative lymphopenia with failure to return to normal for months or even longer was due to the fact that the lymphocyte is very sensitive to radiation effects. The platelet count is a delicate measure of the amount of radiation received, as it is a sensitive indicator of damage to the blood-forming system. The maximum depression of platelets occurred after the fourth week after the bomb test. Purpura may be delayed until this time of low platelet formation. Recovery started in the fifth to sixth week, but a second lesser depression occurred during the seventh and eighth weeks. Even at the end of one year, the platelet counts had not reached normal values.

Morton points out that there is a definite relation between the time elapsing between the exposure to radiation and the onset of symptoms. The most severe radiation resulted in death in 100% of those exposed in from four to ten days after the explosions at Hiroshima and Nagasaki. Vomiting was noted on the day of bombing, with fever, diarrhœa and leucopenia two to seven days later. Purpura developed in from four to seven days. People with less severe exposure show symptoms somewhat later. If diarrhœa, epilation, depressed leucocyte counts and anæmia are noted during the first week after exposure, and fever, purpura and epilation during the second week, death will occur within six weeks in 50% of cases. If depressed leucocyte counts and anæmia are noted within the first two weeks, and mucous membrane ulceration, epilation, purpura, diarrhœa, malaise and weight loss after two weeks, death may occur in up to 90 days in a small proportion of cases. A rough rule for estimating radiation hazards, called the "2-4-6" rule, indicates that 50% of personnel will be sick with no deaths if exposed to 200*r*; 100% will be sick with 50% of deaths if exposed to 400*r*; 600*r* will cause all personnel to be sick, and the mortality will be 100% with a few possible exceptions.

In any atomic explosion two types of irradiation are important. One is from the penetrating gamma rays and neutrons, producing internal body irradiation of mild or severe degree depending on amount, distance, shielding and other factors. The other is the local irradiation of exposed surface areas from beta and soft gamma rays modified according to the factors enumerated. The tissues most sensitive to radiation are the blood-forming system, the sex cells and the gastro-intestinal tract. It has long been known that X-ray treatment is followed by a drop in the number of leucocytes, especially the lymphocytes, and continued exposure results in depression of the whole blood-forming apparatus. Unless there is shielding of the gastro-intestinal tract and of the sex organs, damage will be done by relatively small exposures to radiation.

In total body irradiation of severe degree, cell injury and cell death are noted in the irradiated superficial tissues; this is even more apparent in the radiosensitive organs. The depression of the blood cells removes one of the principal lines of defence against bacterial invasion, which the damage to the gastro-intestinal tract epithelium allows. Again, the failure of coagulation of the blood enhances the spread of the bacterial invaders. After exposure there is a latent period when the patient appears much better than he really is, the radiation effects being insidious.

The acute radiation syndrome is produced by radiations which cause damage to radiosensitive tissue throughout the body. It is a toxic response with a delayed appearance. All types of radiation burns have a similarity in their progression, but there are phases in radiation burns which characterize the acute radiation response. Within the first 48 hours, if the exposure has been severe, erythema, œdema and blanching develop; these may give the symptoms of tingling, burning, itching and stiffness. During the next three to five days no further developments may be noted, but by the sixth to the eighth day secondary erythema may appear with extravasation of blood into the burned areas. In the next two weeks erythema will increase, and vesicles may form and coalesce. At the end of two to three weeks the process becomes quiescent; if the blood supply has not been damaged too much, epithelium grows over the areas which have been desquamated. However, if the blood supply has been damaged, healing does not occur, and chronic ulceration results. In such instances, surgical intervention with excision of the ulcerated areas and skin grafting may help in repairing these areas. Healing without grafting is prolonged, and when it does occur, the epidermis is atrophic without hair or sebaceous glands.

Beta burns from radioactive dust can be prevented by taking cover, by early repeated bathing and by change of clothing. The hair should be shaved off if it retains any of the material. If such early attention is possible, there is little danger of serious injury from the dust, as the amount of gamma exposure constitutes the hazard in these explosions. Treatment must be directed at prevention of infection in the burned areas. When the blood count is dangerously low, transfusion is indicated. The use of antibiotics may be helpful in preventing septicæmia after the resistance to infection has been lowered.

Years later, secondary ulceration may take place from impaired blood supply, with atrophy, hyperkeratosis, telangiectasis and in some cases malignant degeneration.

Late general effects of atomic radiation have been studied in the Japanese survivors of the bombed city explosion. Morton states that Neil and Schull in an exceedingly thorough study of the genetic effects of these bombings were unable to demonstrate any conspicuous genetic effects. Plummer noted microcephaly in intrauterine exposed fœtuses. Slight retardation in growth and development of children born to exposed parents has been demonstrated. This lasted for some four years. A definite increase in leukæmia came five to six years after exposure in the explosions at Hiroshima and Nagasaki. There was also evidence of lenticular defects ("radiation cataracts").

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

OPENING OF A MEDICAL SCHOOL IN SYDNEY.[1]

[From the *Australasian Medical Gazette*, February, 1883.]

THE medical school is preparing for work and opens next month. The general opinion, however, in professional circles is, that its opening could be advantageously deferred for a few years.

An effort has been started with some, though not as yet well assured promise, to establish complete schools of Pharmacy and Dentistry, in affiliation with an "Industrial University"; the latter is, unhappily, very much required.

The Government appears to be very favourably disposed towards the establishment of a "Lock Hospital" in Sydney, and inquiries in this view are now taking place. The matter will be considered in one way or another within a short time.

The Government has placed £32,000 on the estimates towards the construction of the Alfred and Sydney Hospitals. It is reported "quantities" never having been taken out in connection with one of our hospital's buildings, the total will run up to beyond a quarter of a million. An angry feeling on the matter is surging up. It is maintained that before a penny towards such purposes is voted, satisfactory guarantees touching the probable total should always be afforded.

Medical Societies.

THE CARDIAC SOCIETY OF AUSTRALIA AND NEW ZEALAND.

Annual Meeting.

THE annual meeting of The Cardiac Society of Australia and New Zealand will be held on May 25 and 26, 1959, in the Verco Theatre, Institute of Medical and Veterinary Science, Frome Road, Adelaide. On May 27, a plenary session will be held in conjunction with The Royal Australasian College of Physicians. The programme for the scientific sessions of the annual meeting of the Cardiac Society is as follows:

Monday, May 25: 11 a.m., "Differential Pulmonary Blood Flow in Atrial Septal Defect", H. Fleming. 11.20 a.m., "Atrial Septal Defects, with Special Reference to the Septum Primum". (i) "Accurate Assessment", H. P. B. Harvey; (ii) "Surgical Observations", R. Nicks. 2 p.m., "Flow and Systolic Pressure Gradient in Aortic Valve Disease", P. Hetzel. 2.30 p.m., "The Premonitory Syndromes of Complete Heart Block", A. Rae Gilchrist. 3 p.m., "Extension of Myocardial Infarction during Anticoagulant Treatment", A. J. Goble, A. N. O'Brien. 3.45 p.m., "Experiences with Aortic Valvotomy under Direct Vision", K. N. Morris. 4.15 p.m., "Civilized Pattern of

[1] From the original in the Mitchell Library, Sydney.

Human Activity and Coronary Heart Disease", S. Minc (introduced).

Tuesday, May 26: 9 a.m., "Experiences in the Surgical Treatment of Ischæmic Heart Disease", D. Stuckey. 9.30 a.m., "Significance of Intralobular Septal Lines in Mitral Stenosis", M. Begley (introduced). 10 a.m., "The Cellular Basis of the Electrocardiogram", T. E. Lowe. 11 a.m., "Visualization of the Aortic Valve by Cineangiography", G. Sloman (introduced). 11.30 a.m., "Digitalis Intoxication with Particular Reference to Atrial Arrhythmias", I. Prior. 12 noon, "Prolonged Intravenous Heparin Administration in the Treatment of Acute Myocardial Infarction", A. Wynn. 2 p.m., Clinical meeting. 4 p.m., "A Case of Anomalous Pulmonary Venous Drainage into the Inferior Vena Cava", E. Roche. 4.30 p.m., film, "The Jugular Venous Pulse" (National Heart Hospital).

Inquiries regarding the annual meeting should be addressed to Dr. J. M. Gardiner, Honorary Secretary and Treasurer, The Cardiac Society of Australia and New Zealand, Alfred Hospital, Prahran, S.1., Victoria.

Correspondence.

GROWING UP IN A CHANGING WORLD.

SIR: Dr. G. P. O'Day asserts that there is a lower incidence of juvenile delinquency in a socialist society than in a capitalist society. As he does not reveal the standards on which this judgement is based, its validity may be doubted. Nevertheless, even if his assertion could be accepted, there is an explanation which is different from that into which he plunges so enthusiastically.

Under communism, any citizen may, at any time, be seized and carried off to a forced-labour camp. Armed with this power, the Government can thin the ranks of its adverse critics. It can also limit the numbers of any other class of its citizens, who can be removed from public life. In listing the many deficiencies of a capitalist society, Dr. O Day must include this: "There is no similar power for the curbing of juvenile delinquency."

Yours, etc.,

F. PHILLIPS.

174 Macquarie Street,
Hobart.
April 17, 1959.

A NATIONAL BIOLOGICAL STANDARDS LABORATORY.

SIR: I would like to draw your attention to a report published in your Journal, No. 13, of March 28, 1959, concerning an announcement made by the Minister for Health, Dr. Cameron, on the establishment of the National Biological Standards Laboratory and the functions of this laboratory.

From the comments made in the last paragraph of your report on this announcement, it could be implied that the establishment of this laboratory was the first step introduced to control the standards of therapeutic substances. This implication is quite erroneous. The establishment of this Laboratory is, in fact, a further step in a system which has been operating for some time, and not an initial step as your comment would imply.

I would draw your attention to the *Therapeutic Substances Act*. This Act was assented to in 1953, but did not come into operation until 1956, when the regulations to this Act were brought down. Sampling of therapeutic substances under the provisions of this Act has been proceeding since June, 1957. From the inception of this sampling to February, 1959, a total of 498 samples from imports have been analysed.

Furthermore, in the field of pharmaceutical benefits available under the provisions of the *National Health Act*, sampling of both general and pensioner pharmaceutical benefits has been carried out since the inception of the scheme. The following figures are quoted as an example of the scope of this sampling. In the period July 1, 1957, to June 30, 1958, a total of 607 samples were taken from approved chemists and 46 samples from manufacturers. All these samples have been analysed in one or other of the laboratories appointed for the purpose of carrying out these analyses.

As a result of adverse analytical reports, certain brands of products included in the list of pharmaceutical benefits have been removed. It has been found also that there is now less cause for complaint in the dispensing of benfits by approved chemists.

You will realize, therefore, that considerable attention has already been given to the standards of therapeutic substances, and that the establishment of the National Biological Standards Laboratory is simply a further link in this chain of control.

I would be glad if you would correct what I consider to be an incorrect comment in this regard.

Yours, etc.,

A. J. METCALFE,
Director-General of Health.

Commonwealth Department of Health,
Canberra, A.C.T.
April 14, 1959.

HEALTH CARE IN AUSTRALIA.

SIR: We consider that the paragraph "Medical Inspection of School Children" in the article "Health Care in Australia" (Journal, March 21, 1959) presents an inadequate and misleading picture of the functions of a school health service.

The primary object of such a service should be, not the medical examination of children, but the health education of children and parents. To achieve this object, it is necessary that the parent should actually be present at the time of examination, and not merely be notified afterwards of the defects, if any, found. It is essential that there should be an opportunity for the medical officer to discuss with the parent all the factors in the environment that will contribute towards the growth of a healthy citizen; and this is just as important for children showing no "defects" as for those presenting some departure from normal.

There is no excuse for devoting only a limited time to each examination. On the contrary, sufficient time should be allowed to enable each child to be considered as an individual, and for an assessment to be made of that child's health in relation to its surroundings. To provide anything less than this is to provide merely the outward appearance of a school health service, without achieving its real function.

Yours, etc.,

H. M. L. MURRAY,
Director of Public Health;

HEATHER B. GIBSON,
School Medical Officer.

Department of Health Services,
Division of Public Health,
Hobart,
Tasmania.
April 9, 1959.

ŒSOPHAGEAL HIATUS HERNIA.

SIR: In the Journal of April 4, 1959, Dr. S. J. M. Goulston assures us that uncomplicated hiatus hernia can be satisfactorily controlled by conservative therapy. We wish we could accept this comfortable assurance; but, unfortunately, we see many patients who still have pain and dysphagia despite a somewhat irksome medical régime. We believe chronic anæmia, severe hæmorrhage, dysphagia or persistent pain are absolute indications for operation. Stricture complicating œsophagitis is, in our experience, the commonest cause of dysphagia, and many of these patients require the most major surgery for their relief. Conservative treatment palliates, but never cures. Surgery offers complete and lasting cure to the majority of severely handicapped patients. Since 1939 we have operated on over 200 patients, whose age varied from a few weeks to over 90 years. One patient died of a cardiovascular accident; all the others survived operation. In the Journal of July 28, 1956, one of us (K.N.M.) reviewed our results. In the first 25 operations done prior to 1951, the recurrence rate was 50%; but between 1951 and 1956, with better technique, there were only four recurrences in 90 patients who had been followed up.

Even inguinal hernias recur, and cholecystectomy and operations for duodenal ulcer do not cure 100% of patients. Hiatus hernia can be cured by surgery, and operation should not be withheld if symptoms persist despite medical treatment.

In 1956 one of us (K.N.M.) wrote:

> In conclusion I wish to say that I feel that the surgery of hiatus hernia has now advanced to a very satisfactory stage. Mortality and morbidity are extremely low and the recurrence rate is small and will become smaller with increasing experience.
>
> Many of these patients have been miserable for years with chronic dyspepsia, dysphagia or pain. Others have had their lives endangered by massive hæmorrhage, chronic anæmia or œsophageal obstruction. These people are usually given relief that is so complete and dramatic that many of them are among our most grateful patients.

We see no reason to alter this conclusion.

Yours, etc.,

C. J. OFFICER BROWN,
KENNETH N. MORRIS.

Victor Horsley Chambers,
12 Collins Street,
Melbourne, Victoria.
April 13, 1959.

ACUTE OTITIS MEDIA IN CHILDREN: A SURVEY.

SIR: I have always been interested in the subject of otitis media in infants and children, and studied with interest the excellent article by Dr. Patricia Davey and her co-workers in the issue of the Journal of February 28, 1959. However when treatment was described and discussed, I was surprised that there was no mention of the efficacy of the simple operation of adenoidectomy in preventing the recurrence of otitis media.

I always operate if the child has a second attack or if aural discharge persists. This method of attack was taught to me forty years ago by Dr. Frank Andrew, of Melbourne, and Dr. Graham Brown, of Brisbane. It is rare indeed for otitis media to recur after the operation. If the drum is bulging, I do a myringotomy as well. It is many years since I have had to operate on a mastoid.

After adenoidectomy the nasal discharge soon clears up without nasal toilet, which is difficult for a mother to perform on an infant or young child.

Surely adenoids are the commonest cause of blockage of the Eustachian tubes?

Yours, etc.,

E. KENT-HUGHES.

"The Minto",
Rusden Street,
Armidale, N.S.W.
April 12, 1959.

College of Pathologists of Australia.

VICTORIAN BRANCH: SCIENTIFIC MEETING.

THE Victorian members of the College of Pathologists of Australia will hold a scientific meeting on Friday, May 15, 1959, at 5.15 p.m. in the Royal Society Hall, 9 Victoria Street, Melbourne.

The guest speaker will be Dr. George L. Wied, Associate Professor of Obstetrics and Gynæcology in the University of Chicago, and his subject will be "The Scope of Cytology". Fellows and Members of the other Colleges, as well as all medical practitioners interested in cytology, are invited to attend.

Naval, Military and Air Force.

APPOINTMENTS.

THE following appointments, changes etc., are published in the *Commonwealth of Australia Gazette*, No. 17 of March 5, 1959.

NAVAL FORCES OF THE COMMONWEALTH.

Appointment.—David Alexander Noble is appointed Surgeon Lieutenant (for Short Service) (on probation), dated 5th January, 1959.

Termination of Appointment.—The appointment of George Grahame Mahony, as Surgeon Lieutenant (for Short Service), is terminated, dated 26th December, 1958.

Citizen Naval Forces of the Commonwealth.

Royal Australian Naval Reserve.

Promotions.—Surgeon Lieutenant William George Tellesson is promoted to the rank of Surgeon Lieutenant-Commander, dated 21st December, 1958.

Royal Australian Naval Volunteer Reserve.

Termination of Appointments.—The appointments of the following are terminated, to date 1st March, 1958: Surgeon Lieutenant-Commanders Stewart Horton Delbridge Preston, Norman Alfred Richards and Peter Donald Graeme Fox.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Course for the Primary F.R.A.C.S. Examination.

A PART-TIME refresher course in anatomy, physiology and pathology, suitable for candidates proceeding to the Primary F.R.A.C.S. examination, has been organized and arranged by the New South Wales State Committee of the Royal Australasian College of Surgeons. The course, which will be under the supervision of Mr. E. V. Barling, will begin in Sydney on Monday, June 8, 1959, and continue for a period of approximately ten weeks, concluding in August prior to the Primary Fellowship examination on September 3. It will be held in the New Medical School of the University of Sydney in the late afternoons only, and will take the form of tutorials. The management of the course will be undertaken by The Post-Graduate Committee in Medicine in the University of Sydney. The fee for attendance is 25 guineas. Applications will close on Wednesday, May 27, and should be addressed to the Course Secretary, The Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney. Telephones: BU 4497-8. Telegraphic Address: "Postgrad Sydney".

University Intelligence.

THE UNIVERSITY OF SYDNEY.

DR. JOHN READ, M.D., B.S., M.R.A.C.P., has been appointed Senior Lecturer in Medicine in the University of Sydney. Dr. Read graduated from the University of Sydney in 1952 with first-class honours and the University Medal. After holding resident appointments at the Royal Prince Alfred Hospital, he carried out experimental studies on the role of immune mechanisms in the production of certain pulmonary lesions, working in the Department of Pathology, University of Sydney, during 1956-1957. In the latter part of 1957 he investigated methods of assessing uneven pulmonary ventilation, working in the Department of Medicine. These studies were extended to the interrelation between pulmonary ventilation and blood flow at the Postgraduate Medical School of London during 1958, as Wunderly Travelling Scholar of The Royal Australasian College of Physicians. He has been an Honorary Assistant Physician at Sydney Hospital since 1957.

Dr. Lyal Watson, M.B., B.S., M.R.A.C.P., has been appointed Senior Lecturer in Medicine in the University of Sydney. After graduating with honours from the University of Sydney in 1949, he was appointed resident medical officer and then registrar at the Royal Prince Alfred Hospital, Sydney. In 1954 he began an investigation of mechanisms concerned in the neurological manifestations of hypocalcæmia, working in the Clinical Research Unit of the Royal Prince Alfred Hospital with the aid of a grant from the National Health and Medical Research Council of Australia. In 1955 he was appointed Honorary Assistant Physician at Sydney Hospital. During 1957 and 1958

he continued his studies of disorders of metabolism in the Medical Unit, University College Hospital, London, as holder of the Travelling Scholarship in Medicine of The Royal Australasian College of Physicians and subsequently as recipient of a grant from the Adolph Basser Research Funds of the College.

Appointment of Two Associate Professors.

The Senate of the University of Sydney has made appointments to Associate Chairs of Cardio-Pulmonary Physiology and Medical Statistics.

Dr. P. I. Korner, who is at present Senior Lecturer in Physiology, has been appointed Associate Professor of Cardio-Pulmonary Physiology. Dr. Korner is a graduate of the University of Sydney, having been awarded the degree of Bachelor of Science with first-class honours in physiology in 1947, Master of Science in 1948, Bachelor of Medicine and Bachelor of Surgery with second-class honours in 1951, and Doctor of Medicine in 1956. He went abroad some years ago as the first Australian and New Zealand Life Insurance Medical Research Fellow and worked both at the Post-Graduate Hospital in London and at the Harvard Medical School in Boston, U.S.A. While abroad he devised the first method for measuring the amount of blood which flows back into the heart as a result of valvular incompetence. He returned to the University of Sydney in 1956 and has built up a research unit for investigating problems concerned with the heart, lungs and circulation. His work in these fields has earned for him an international reputation. Dr. Korner has been selected by the Royal Society of New South Wales for the award of the 1958 Edgeworth David Medal; this medal is awarded every third year to a scientist who has made distinguished contributions to knowledge of the biological or earth sciences.

Dr. H. O. Lancaster has been appointed Associate Professor of Medical Statistics. Dr. Lancaster is also a graduate of the University of Sydney, having been awarded the degrees of Bachelor of Medicine and Bachelor of Surgery with second-class honours in 1937, Bachelor of Arts in 1947, and Doctor of Philosophy in 1954. He was appointed to his present position of Senior Lecturer in Medical Statistics in 1955, having been previously Lecturer in Preventive Medicine. He served as a major in the Australian Army Medical Corps during the whole of the period of the second World War, and has built a considerable reputation for his work in medical statistics.

Notes and News.

Department of Immigration.

THE Department of Immigration, Canberra, has requested publication of the following advice to hospitals and other institutions:

Hospitals and other institutions proposing to recruit staff from outside Australia should remember that immigration requirements have to be met, and it would save possible embarrassment if the Commonwealth Department of Immigration were first told in what countries it is proposed to advertise, so that the Department can outline the circumstances in which nationals of those countries may or may not be permitted to enter Australia.

Medical Appointments.

THE undermentioned appointments have been made at the Royal Adelaide Hospital, Adelaide:

Dr. E. F. West has been appointed Honorary Consulting Orthopædic Surgeon.

Dr. N. P. Wilson has been appointed Honorary Orthopædic Surgeon.

Dr. G. A. Jose has been appointed Honorary Assistant Orthopædic Surgeon.

Dr. P. R. Hodge has been appointed Honorary Clinical Assistant in the Department of Pathology.

Dr. A. W. J. Lykke has been appointed Honorary Clinical Assistant in the Department of Pathology.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED APRIL 4, 1959.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1(1)	..	..	..	..	..	..	..	1
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	3	..	3
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	5(1)	15(14)	..	..	..	..	1	..	21
Diphtheria	..	1	..	..	..	..	..	..	1
Dysentery (Bacillary)	..	3(3)	..	1(1)	1(1)	..	1	..	6
Encephalitis	1	..	..	..	..	..	..	..	1
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	54(16)	23(16)	7(6)	4(3)	2(2)	..	1	1	92
Lead Poisoning	..	..	..	..	..	..	1	..	1
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	2	..	..	..	..	..	2
Malaria	..	1(1)	2(2)	..	..	..	..	..	3
Meningococcal Infection	..	..	..	..	..	..	2	..	2
Ophthalmia	..	..	..	..	3	..	..	..	3
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	1	..	..	..	..	..	..	..	1
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	1(1)	2(1)	..	..	..	..	..	..	3
Puerperal Fever	1(1)	..	..	..	..	..	..	..	1
Rubella	..	24(19)	..	..	3(3)	..	..	..	27
Salmonella Infection	..	..	..	..	2(1)	..	..	..	2
Scarlet Fever	21(11)	28(23)	2	2(2)	..	1	..	..	54
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	1(1)	1	..	..	..	..	..	2
Trachoma	..	..	..	..	69(3)	..	207	..	276
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	8(8)	12(8)	10(3)	2(1)	5(3)	2(1)	..	..	37
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Dr. R. W. L. Crosby has been appointed Honorary Clinical Assistant in the Dermatological Department.

Dr. P. J. Stobie has been appointed Honorary Clinical Assistant in the Ophthalmological Department.

Dr. J. B. Hughes has been appointed Honorary Clinical Assistant in the Department of Anæsthesia.

Dr. R. F. Condon has been appointed Honorary Clinical Assistant in the Department of Anæsthesia.

Dr. P. R. Hodge has been appointed Honorary Clinical Assistant in the Department of Pathology at the Queen Elizabeth Hospital, Adelaide.

Notice.

VICTORIAN BRANCH B.M.A.: PREVENTIVE MEDICINE SECTION.

THE talk which was to be given by Dr. Alan Ferris to the Preventive Medicine Section of the Victorian Branch (B.M.A.) on Thursday, May 14, 1959, at 4.30 p.m., has been deferred. Instead, a talk will be given on Thursday, May 28, 1959, at 4.30 p.m., in the Medical Society Hall, 426 Albert St., East Melbourne, by Dr. F. Clements, of the Royal Alexandra Hospital for Children, Sydney. His subject will be "Goitre and Goitrogens". All members are invited to attend.

Nominations and Elections.

THE undermentioned have applied for election as a members of the New South Wales Branch of the British Medical Association:

Blumer, Robert George, M.B., B.S., 1957 (Univ. Sydney), 90 Stanhope Road, Killara, New South Wales.

Farkas, George Steven, M.D., 1951 (Univ. Budapest) (registered in accordance with the provisions of Section 17 (2A) of the *Medical Practitioners Act*, 1938-1958), 24 Bellevue Road, Bellevue Hill.

Shanahan, Leo Francis, M.B., B.S., 1955 (Univ. Sydney), 96 Molesworth Street, Lismore, New South Wales.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association: Burgheim, Eva, M.B., B.S., 1959 (Univ. Sydney); Faunce, Edmund Alured de Laune, M.B., B.S., 1959 (Univ. Sydney); Moulton, William Kirton, M.B., B.S., 1959 (Univ. Sydney); Rigney, John Gilbert, M.B., B.S., 1959 (Univ. Sydney); Taylor, Jill Argent, M.B., B.S., 1959 (Univ. Sydney); Bridger, Allan Joseph, M.B., B.S., 1956 (Univ. Sydney); Cook, Peter, M.B., B.S., 1953 (Univ. London); Greening, Dorothy Grace, M.B., B.S., 1956 (Univ. Sydney); Johnston, Colin Ivor, M.B., B.S., 1958 (Univ. Sydney); Leckie, Robert David, M.B., B.S., 1954 (Univ. Sydney); Levi, Louis, M.B., B.S., 1955 (Univ. Sydney); Opie, Peter Bruce, M.B., B.S., 1956 (Univ. Adelaide); Phillips, John Keith Andrew, M.B., B.S., 1957 (Univ. Sydney); Thompson, William Kenneth Allen, M.B., B.S., 1953 (Univ. Sydney); Colja, Michael, M.D., 1952 (Univ. Yugoslavia) (regional registration); Hollo, Stephen Julian, M.D., 1950 (Univ. Budapest) (registered in accordance with the provisions of Section 17 (2A) of the *Medical Practitioners Act*, 1938-1958); Moser, Rudi, M.D., 1924 (Univ. Berlin) (registered in accordance with the provisions of Section 17 (2B) of the *Medical Practitioners Act*, 1938-1958).

The undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Fox, Bruce Spafford Owen, M.B., B.S., 1958 (Univ. Adelaide), 29 Goyder Street, Erindale, South Australia.

Liddell, Robert Victor, M.B., Ch.B., 1923 (Univ. Edinburgh), 7 West Terrace, Quorn, South Australia.

Altmann, Frank William, M.B., B.S., 1958 (Univ. Adelaide), 29 Goyder Street, Erindale, South Australia.

Moore, Colin Eugene, M.B., B.S., 1958 (Univ. Adelaide), 22 Avenue Road, Highgate, South Australia.

Ancell, Brian Edward John, M.B., B.S., 1957 (Univ. Adelaide), 913 South Road, St. Marys, South Australia.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association: Rice, Michael Scollin, M.B., B.S., 1958 (Univ. Adelaide); Beumont, Gordon Dean, M.B., B.S., 1958 (Univ. Adelaide); Auricht, Clive Oswald, M.B., B.S., 1958 (Univ. Adelaide); Slavotinek, Anthony Hynek, M.B., B.S., 1958 (Univ. Sydney).

Deaths.

THE following death has been announced:

TEECE.—Lennox Graham Teece, on April 23, 1959, at Lyons, France.

Diary for the Month.

MAY 12.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
MAY 14.—New South Wales Branch, B.M.A.: Public Relations Committee.
MAY 18.—Victorian Branch, B.M.A.: Finance Subcommittee.
MAY 19.—New South Wales Branch, B.M.A.: Medical Politics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales. Anti-Tuberculosis Association of New South Wales.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this Journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

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